



# BULLETIN

## OF THE NEW YORK ACADEMY OF MEDICINE

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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



JANUARY 1939

HEMOPHILIA

*The Wesley M. Carpenter Lecture\**

WILLIAM H. HOWELL

**T**HE early history of hemophilia is given by Nasse,<sup>1</sup> Bulloch and Fildes - Schloessmann and others.<sup>1</sup> The disease was first definitely described by Dr. John C. Otto<sup>2</sup> of Philadelphia in 1803. His cases and the subsequent fuller collections made by Nasse give rise to an abundant clinical literature which in time has been followed by extensive experimental investigations starting with the important researches of Sahl<sup>3</sup> in 1905.

The literature up to 1911 has been reviewed critically in the very valuable memoir of Bulloch and Fildes<sup>2</sup> published in that year by the Francis Galton Laboratory for National Eugenics as Parts 5 and 6 of their collection of family pedigrees "illustrating the inheritance in man of mental and physical characters."

These authors sum up their conclusions in the definition that "hemophilia is an inherited tendency in males to bleed." The definition emphasizes what they considered to be the three cardinal characteristics of the disease, namely, the tendency to bleed, the fact that this tendency is inherited and that it is limited to males. It had been further demonstrated

\* Delivered November 3, 1938, in the Eleventh Annual Graduate Fortnight.

at this time that the disease is inherited through the female in accordance with the law of Nasse,<sup>1</sup> which, in substance, states that the disease is limited to the male but is transmitted from the male through an unaffected daughter to a grandson. Since 1911 two further conclusions in regard to the disease have met with general acceptance. First, that hemophilia, in the Mendelian nomenclature, behaves as a sex-linked recessive factor, second, that its outstanding diagnostic characteristic is an abnormally prolonged coagulation time of the blood.

The statement that hemophilia is transmitted as a sex-linked recessive means that the factors or genes responsible for its development are contained in the X chromosome of the reproductive cells. This conception enables us to understand the law of Nasse and to predict under what conditions of mating hemophilia may appear in the offspring. The formulae by means of which such predictions may be made are given in the accompanying diagrams. It is assumed that the ovum contains a pair of X-chromosomes (XX), while the spermatozoon has only a single X-chromosome, as a member of the XY pair, the Y-chromosome apparently not carrying sex genes. At the reduction division which takes place during the maturation of the germ-cell each matured ovum will contain a single X-chromosome, but the spermatozoa fall into two groups, one containing an X-chromosome and one without, having instead a Y-chromosome. In the subsequent combination of these sex cells that takes place in fertilization two groupings of the sex-chromosomes are possible. One of these, an XX pair, leads to the development of a female, the other, an XY pair (or a single X-chromosome) gives rise to a male. If in such a mating the male happens to be a hemophiliac then by theory the X-chromosome in his spermatozoa contains the factor for the disease, and in his marriage to a normal female the defect will be transmitted to some of his children. Theoretically, the combination of sex cells will give rise to fertilized ova containing a single normal X-chromosome, which will develop into males, and others, containing a pair of X-chromosomes, one of which carries the hemophilic factor, which will develop into females. Consequently all of his sons will be normal in the sense that they are free of the hemophilic factor, and they will not be capable of transmitting the disease. All the daughters, on the contrary, will have the hemophilic factor. They will not themselves be bleeders since the ovum contains one normal X-chromosome which is dominant in development, but they will be carriers or conductors of the defect and capable of transmitting it to

HEMOPHILIC MALE + NORMAL FEMALE



- |       |                    |
|-------|--------------------|
| 1. XX | CONDUCTOR DAUGHTER |
| 2. XX | " "                |
| 3. XY | NORMAL SON         |
| 4. XY | " "                |

FIGURE 1

NORMAL MALE + CONDUCTOR FEMALE



- |       |                    |
|-------|--------------------|
| 1. XX | NORMAL DAUGHTER    |
| 2. XX | CONDUCTOR DAUGHTER |
| 3. XY | NORMAL SON         |
| 4. XY | HEMOPHILIC SON     |

FIGURE 2

HEMOPHILIC MALE + CONDUCTOR FEMALE



- |       |                     |
|-------|---------------------|
| 1. XX | CONDUCTOR DAUGHTER  |
| 2. XX | HEMOPHILIC DAUGHTER |
| 3. XY | NORMAL SON          |
| 4. XY | HEMOPHILIC SON      |

FIGURE 3

some of their sons, as is indicated in Figure 2, which indicates what may be expected from the marriage of a conductor female to a normal male. Some of her sons may be hemophiliacs and some of her daughters may be conductors, theoretically a fifty-fifty chance in each case.

These predictions fall in with the facts actually known in regard to the transmission of the disease. A hemophilic male married to a normal female never has hemophilic sons, nor, so far as is known, do any of his descendants through his sons suffer from the disease. On the other hand, his daughters' sons frequently exhibit hemophilia and his daughters' daughters may continue to act as conductors and thus pass on the defect in latent form through many generations.

If it should happen that a hemophilic male married a conductor female, then, according to theory he might have a hemophilic daughter as well as a hemophilic son. As Figure 3 indicates, there would be an even chance for the daughters to be conductors or active hemophiliacs.

As a matter of fact no authentic case of a female bleeder is known. Many such cases have been described, but Bulloch and Fildes<sup>2</sup> who reviewed the literature up to 1911, and Bucur<sup>1</sup> and Schloessmann<sup>3</sup> who have discussed the point for the later literature, agree that the evidence is unsatisfactory. What has been described as hemophilia was more probably purpura or some hemorrhagic condition other than hemophilia. In no case were the data given entirely convincing. It seems quite probable that bleeder-conductor marriages may have occurred occasionally among the known hemophilic families inhabiting a certain district, but Schloessmann was able to find only one clear case among the pedigrees on record. In that case the progeny was too small, one son and one daughter, to constitute a crucial test of the theory. The daughter was not hemophilic—whether she was a conductor is not known since there is no record of her marriage. In view of the interest the question has aroused it seems likely that if any clear-cut case of a female hemophiliac has occurred it would have been made a matter of record. That no case has actually been observed may be due solely to the accident that bleeder-conductor marriages are rare, and if they occur the daughters, if any, have an equal chance of being conductors rather than bleeders. Still the apparently complete absence of such cases has aroused comment and has led to the suggestion that there may be some fundamental biological reason operating against their development. Bauer<sup>8</sup> has suggested, for example, that the hemophilic genes may act as a lethal factor (or be associated with a

lethal factor) and that a double dose of this factor, such as would occur in the ovum destined to produce a female bleeder, would make development impossible.

Although hemophilia is so clearly an hereditary disease there is evidence that sporadic cases occur in which inheritance cannot be demonstrated. Bulloch and Fildes discuss the matter briefly and express the opinion that fewer such cases would be reported "if the authors had had sufficient time, interest or perseverance to investigate beneath what might be immediately apparent upon the surface." They refer however specifically to one pedigree that published by Gettings, which seems to establish the point. In a family of eleven children, six boys and five girls, five of the boys were hemophiliacs. Examination of the medical histories of the direct and collateral ancestry through three generations disclosed no case of hemophilia. Davidson and McQuarrie<sup>1</sup> cite a similar instance in which an only child, a son, was hemophilic. None of the members of either family traced back through three or four generations gave any evidence of the disease although on the maternal side there were ten males who might have been subject to hemophilia according to Nasse's law. Schloessmann<sup>2</sup> discusses the matter at considerable length. He discounts many of the reported cases on the ground that sufficient inquiry was not made into the family histories, but he admits that cases of genuine hemophilia may occur apparently *de novo*. In such cases the symptoms are essentially identical with those of hereditary hemophilia. They seem to be exactly the same disease. It is difficult to believe that in such cases the disease has developed *de novo* in the individual as an acquired characteristic that will disappear at his death, especially as in some of the recorded cases, that of Gettings, for example, it has appeared in two or more males of the same family. One inclines rather to the alternative view that it is a true hereditary condition which has arisen *de novo* by a mutation of the sex-cells of the mother. From this point of view sporadic cases mark the beginning of a new hemophilic strain. Such presumably was the origin of the known hemophilic families that are on record. However, so far as I can ascertain, actual histories, that might support this theory, are lacking in regard to the descendants of known sporadic cases.

In regard to the second point, noted above, namely the prolongation of the clotting time of the blood, it was known to the early observers that hemophilic blood clots slowly, but in their observations emphasis was laid upon the obstinate character of the bleeding. Sahli<sup>3</sup> was the first to



study systematically variations in the clotting time and since his investigations experimental work has been concentrated chiefly upon the solution of this problem. It is true that many investigators have expressed their belief that the prolonged clotting time is not in itself sufficient to account for the long continued hemorrhages exhibited by the hemophilic. It has been suggested that there must be also some structural or functional abnormality in the walls of the blood vessels or in the tissues generally to account for the prolonged bleeding, especially as it has been asserted by several good observers that bleeding, traumatic or after operation, may continue when the coagulation time is normal.

The few cases in the literature in which a normal coagulation time has been recorded for hemophilic blood are open to question on the ground of inadequate technique. For while the procedure of determining clotting time is simple, the process of clotting is apparently subject to large variations from very small changes in conditions. It is now generally recognized that methods in which the specimen of blood is obtained by pricking or stabbing the skin are unreliable on account of the possibility of admixture of more or less of thromboplastic substance from the tissues. Since the older observers used this method their results can not be accepted without confirmation. The usual practice at present is to remove the sample of blood by venipuncture with a syringe, but with this method also duplicate samples may show considerable variation in time of clotting. Failure to enter the vein promptly at the first insertion may result in the accumulation of some tissue juice in the needle which will affect the time of clotting. Some of the contradictory results found in the literature are probably to be explained by errors of this kind in the technique.

With regard to pathological changes other than the lengthening of the time of coagulation it may be said that none has been definitely demonstrated. Claims of various kinds have been made with regard to differences in vascular structure or function, or in thromboplastic content of the tissues, or in the composition of the blood, but they have either failed of confirmation at the hands of other observers, or they seem to be lacking in significance. It is possible that some of the minor differences that have been noted, such as the higher chloride content of hemophilic blood, may prove later to be of importance, but at present the one pathological condition that is definitely established and that is directly connected with the hemorrhages of hemophilia is the prolonged clotting time of the blood. Those who have had the widest experience with

hemophilic patients believe that the severity of the disease is in general proportional to the delay in coagulation. On the other hand it is known that remedial measures such as blood transfusions, which serve to control the hemorrhages tend to restore the coagulation time to or toward the normal. It is believed therefore that a definite prolongation of the clotting time is diagnostic of hemophilia and serves to differentiate it from other hemorrhagic conditions especially from thrombocytopenic purpura with which it has often been confused. Ordinarily at least the distinction between these two conditions is easily made. In hemophilia the clotting time is prolonged but the platelet count is normal. In thrombocytopenic purpura the coagulation time is normal while the platelet count is much reduced. There is also a difference in the character and location of the hemorrhages. It is interesting to note however, that several authors have reported cases of a seemingly intermediate character which indicate the possibility of some kind of a connection between the two conditions. Pickering<sup>10</sup> describes a case in which during the period of observation, about two years the patient seemed to oscillate periodically between hemophilia and purpura—at one time a coagulation time of forty to sixty minutes and a platelet count of 340,000, and a year later a normal clotting time of eleven to twelve minutes but a platelet count of 84,000. Minot and Lee<sup>11</sup> report a similar experience. Some of their cases they say, “at one time may show a normal platelet count but a marked delay of the coagulation time while at other times the coagulation time may be less delayed while the blood-platelets are only few in number.” In one such case in my own experience the hemorrhages were of the hemophilic type, affecting the joints, and the coagulation time was somewhat prolonged, twenty-six minutes, but at the same time the platelet count was quite low, 64,000. The patient gave no family history of hemophilia. Unfortunately none of these cases has been followed over an adequate period of time and with reference to their family histories. Their significance remains uncertain but they do suggest caution in making a positive distinction between the two conditions. It may be said that a prolonged coagulation time is found in all cases of undoubted hemophilia, but, used as a diagnostic test, it should be supported by collateral evidence based upon the character of the hemorrhages or the family history.

Data are lacking in regard to the amount of delay in coagulation which may be considered as indicative of a hemophilic state. Indeed we have no satisfactory information in regard to the variations in this respect

that may be exhibited by the blood of normal persons. We can not well compare figures published by different authors owing to variations in the methods used. No observer, so far as I know, has made extensive observations of this kind under varying conditions of health and disease using acceptable and consistent technique throughout.

Schloessmann<sup>1</sup> gives data for twenty of his hemophilic patients. The samples of blood were obtained by venipuncture and the coagulation time was determined by Burkner's method for which the normal is stated to be five and one-half minutes at 25° C. His results showed coagulation times varying from thirteen minutes to two and one-half hours, and the author concludes that among hemophiliacs the coagulation time is an individual characteristic that shows wide variations. Reports from other investigators indicate in general a longer time than is given in Schloessmann's figures. In the cases that I have examined the coagulation time has never been less than an hour and reports in the literature vary usually from about an hour to as much as twelve hours or more.

For any one individual the coagulation time is subject to irregular changes for reasons that are not apparent. Schloessmann<sup>1</sup> believes that these variations are practically of little importance and for the most part fall within the limits of error of the method. But this has not been my experience and his view is not I think supported by reports from other workers. With three of my cases I have been in quite close contact for a period of about twenty-five years, and during that time I have had many occasions to determine the coagulation time. All three have shown variations that lie well beyond possible limits of error of the method. In one of these cases who has served as a laboratory assistant a record was kept of 150 determinations extending over several years. The times of coagulation varied from about one hour to four hours, with an average of two hours and twenty minutes. Feissly's<sup>12</sup> tables show more extensive variations and in the curves for seven patients published by Stetson, Forkner, Chew and Rich,<sup>13</sup> covering a period of a few months, variations as much as from one to twelve hours are noted. In my own cases I have not been able to satisfy myself that spontaneous attacks of joint bleedings, which have occurred at irregular intervals, were associated with the times of slower coagulation. Whatever the condition may be that is responsible for the retarded coagulation of hemophilic blood it is evidently subject to frequent and considerable variations. It is conceivable therefore that at times the process might approach or reach a normal period, but as has

been pointed out there is no good evidence that this ever occurs. The time of coagulation is always in excess of the normal.

All recent experimental investigations have been concentrated upon an effort to determine the factor or factors responsible for the retarded coagulation. There seems to be no question that the fibrinogen in hemophilic blood is present in normal amount and exhibits normal properties, on addition of active thrombin the blood clots promptly. There is general agreement that the delay in clotting is due to some abnormality in the factors or processes concerned in the formation of thrombin. Theoretically the delay might be due to the existence of an inhibitory substance or to some change in quantity or properties of the three known thrombin factors: prothrombin, calcium and thromboplastic substance. All of these hypotheses have been made by one worker or another and each has supported his views by experimental evidence. Time does not permit me to refer specifically to all the theories that have been proposed. The one that has perhaps met with most approval and support by workers, in this country at least, is that advanced by Addis.<sup>11</sup> His experiments led him to suggest that the prothrombin is at fault. While present in normal amount it is qualitatively different in that it is less reactive and hence is converted to thrombin more slowly. The experiments published by Addis in support of this hypothesis while seemingly conclusive are, I believe, open to criticism. Prothrombin precipitated from hemophilic plasma by  $\text{CO}_2$  was found to be less reactive than similar preparations from normal plasma. But the  $\text{CO}_2$  method precipitates from plasma fibrinogen and thromboplastic material as well as prothrombin. In Addis's experiments the fibrinogen was removed but the thromboplastic substance was left. The effect of this latter substance on the clotting time was ignored on the assumption that it exists in equal amounts in normal and hemophilic plasma. This assumption is not justified as has been abundantly shown by recent work which will be referred to later. Addis was led into error on this point because his previous experiments had convinced him that in normal and hemophilic serum the amounts of thromboplastic substance are the same, but proving this point for serum does not establish it for plasma. In the serum of hemophilic blood the platelets have all disintegrated and yielded their quota of thromboplastic material. It is now known that the plasma of hemophilic blood contains less thromboplastic substance than that of normal blood. If equal amounts of the two plasmas are diluted and precipitated by  $\text{CO}_2$  more thromboplastic substance

comes down with the prothrombin in the normal blood and this fact is sufficient explanation why the prothrombin is activated more promptly by calcium than in the case of hemophilic blood. The same criticism applies to Eagle's<sup>15</sup> confirmation of Addis's results, since his prothrombin was prepared essentially by the same method.

Making use of the acetone method, Howell and Cekada<sup>16</sup> were not able to find any significant difference in quantity or reactivity between prothrombin from normal blood and that from hemophilic blood, and Frank and Hartmann<sup>17</sup> report that prothrombin (proserozyme) from hemophilic blood clots a fibrinogen solution (phosphated plasma) as promptly as prothrombin from normal blood. Nevertheless normal blood contains something, other than prothrombin which is lacking or deficient in hemophilic blood. Frank and Hartmann emphasize a fact which had been noted previously by Sahl<sup>18</sup> and others, namely, that hemophilic blood can be made to clot promptly if normal human plasma is added to it in small amounts, even when the normal plasma has been deprived of its prothrombin by the action of calcium phosphate. They gave to this result the interpretation that normal plasma contains an activator of some kind which facilitates the formation of thrombin and which is absent or deficient in amount in hemophilic blood.

More recently this reaction has been investigated in this country by Patek and Stetson,<sup>18</sup> Patek and Taylor and Pohle and Taylor<sup>19</sup> and in Holland by Bendien and Van Creveld.<sup>20</sup> Starting with the fundamental fact that normal citrated blood added to hemophilic blood, even in quite small quantities, reduces the coagulation time of the latter to the normal range, for example from 170 minutes to 15 minutes, these workers have demonstrated that the active substance concerned can be isolated by precipitating the plasma, after dilution, by acid added to a pH of 5.3 to 5.8. Extracts of this precipitate, before or after drying, in physiological salt solution when added to hemophilic blood cause a marked shortening of its coagulation time. If a hemophilic plasma is treated in the same way a similar precipitate is obtained but its extracts have a distinctly smaller effect in accelerating the clotting of hemophilic blood, showing that the hemophilic plasma contains less of the active substance. Solutions of the active substance thus prepared give protein reactions (they may in fact contain some prothrombin or fibrinogen) and Patek<sup>18</sup> assumes that the active material is a protein body of a globulin nature, which he designates as "globulin substance" and which is closely associated with prothrombin.

Bendien and Van Creveld<sup>19</sup> obtain essentially similar results, they give the name of coagulation globulin to the active material and believe that it is associated closely with fibrinogen although they state that the globulin is to be considered only as a carrier of the active material, since when hemophilic blood is treated in the same way a globulin fraction of a similar amount is obtained which has but little activity in promoting the clotting of hemophilic blood. Experience has shown that this globulin substance or coagulation globulin when injected intravenously into a hemophilic is effective in causing a reduction in clotting time similar to that obtained from transfusions of normal blood. According to Pohle and Taylor<sup>11</sup> the same or a similar result may be obtained from intramuscular injections but Bendien and Van Creveld<sup>20</sup> report that they could get no therapeutic effects from their solutions when given intramuscularly or when fed by mouth.

All this recent work furnishes therefore, good evidence for the view that blood plasma contains a specific substance which accelerates the process of clotting and which is present in smaller amounts in hemophilic blood. It seems entirely probable that the deficiency of this material in the plasma of hemophilic blood is responsible for its delayed clotting and it becomes important to learn as much as possible about its nature and properties and its origin and fate in the body. I have been engaged for the past two years in work of this kind and would like to present briefly some of the results obtained. For the sake of convenience it is desirable to give the substance a provisional name until such time as its chemical nature is determined. The names already suggested, globulin-substance or coagulation-globulin seem to me to be inappropriate since they imply that it is protein in nature and, as I shall show later, this is not correct. The substance in fact is essentially the same material as that designated by Morawitz as thrombokinase. They have the same distribution and properties, such as loss of activity on standing, and probably the same mode of action, but this term carries the significance given to it by Morawitz of a heat labile protein with enzyme-like properties. Among other names suggested hitherto to designate the material in the blood or tissues which accelerates the formation of thrombin, that of thromboplastin is perhaps the most appropriate, since it is a convenient and non-committal abbreviation for the phrase thromboplastic substance. Hereafter in this paper I shall speak of this as plasma thromboplastin and designate the similar or identical substance occurring in the tissues as tissue thromboplastin.

Plasma thromboplastin, as we have seen, may be obtained in crude form from ovalated or citrated plasmas, after dilution, by saturating with  $\text{CO}_2$  or by adding acid to a pH of about 5.5. The precipitate obtained contains prothrombin and fibrinogen as well as thromboplastin, but the activity of its extracts in clotting hemophilic blood is not due to either the prothrombin or the fibrinogen. Extracts may be made which are active but which contain neither prothrombin nor fibrinogen—glycerol extracts for example. Moreover the substance may be prepared equally as well from plasma in which the prothrombin has been removed by treatment with magnesium hydroxide or calcium phosphate, or from plasmas in which the fibrinogen has been removed by heat coagulation at  $56^\circ\text{C}$ . It is easy to show that not all of the plasma thromboplastin is removed by precipitation with acid. The plasma that is left, when neutralized, still shows the property of hastening the coagulation of hemophilic blood. If the globulins of the plasma are fractionated by precipitation with ammonium sulphate at various concentrations, 25 per cent, 33 per cent, 50 per cent and finally the serum albumin by addition of acid, all the precipitates on examination will show the presence of some plasma thromboplastin. It seems to be associated with, or, at least, be precipitated with all the proteins of the plasma although most of it in normal plasma comes down with the fibrinogen and the euglobulin fraction. If fibrinogen is prepared from normal plasma by precipitation with ammonium sulphate added to a concentration of 25 per cent, instead of by acid, the precipitation being repeated several times, the final solution of purified fibrinogen in physiological saline has a marked accelerating effect upon the clotting of hemophilic blood. If the fibrinogen in such a solution is removed by heating to  $56^\circ\text{C}$ , the solution remaining after filtration shows the same coagulating action upon hemophilic blood. If the fibrinogen is associated in any way with the thromboplastin, the union is broken when the fibrinogen is denatured and precipitated by heat.

My experiments corroborate those of previous observers in indicating that plasma thromboplastin is present in smaller amounts in hemophilic than in normal blood. In the cases that I have used in my experiments the difference was not so great as has been noted by other observers, but it was very distinct and invariable when the concentrations used were not so strong as to obscure the relations. Hemophilic blood is not entirely lacking in thromboplastin, but it contains less of it. The difference in this respect between it and normal blood might well be used as an addi-

tional diagnostic test. The method used was to oxalate equal amounts of normal and hemophilic blood and remove the corpuscles by centrifuging. The clear plasma was diluted ten times with distilled water and was then precipitated by  $\text{CO}_2$  or by the addition of dilute acetic acid. The precipitates obtained by centrifuging were washed with distilled water and then extracted with physiological saline made neutral or slightly alkaline with sodium bicarbonate. With solutions prepared in this way such comparative results as the following were obtained:

1. Hemophilic blood 0.5 cc + thromboplastin extract of normal plasma 0.3 cc clot in three minutes.  
Hemophilic blood 0.5 cc + thromboplastin extract of hemophilic plasma 0.3 cc clot in eight and one-half minutes.  
Control Hemophilic blood 0.5 cc + physiological saline 0.3 cc, clot in ninety-five minutes.
2. Hemophilic blood 0.5 cc + thromboplastin extract of normal plasma 0.3 cc clot in four minutes.  
Hemophilic blood 0.5 cc + thromboplastin extract of hemophilic plasma 0.3 cc clot in twelve and one-half minutes.  
Control Hemophilic blood 0.5 cc + physiological saline 0.3 cc, clot in eighty-five minutes.
3. Hemophilic blood 0.5 cc + thromboplastin extract of normal plasma 0.3 cc clot in 19.5 minutes.  
Hemophilic blood 0.5 cc + thromboplastin extract of hemophilic plasma 0.3 cc, clot in 47.5 minutes.  
Control Hemophilic blood 0.5 cc + physiological saline 0.3 cc, clot in ninety minutes.

In the last experiment the extracts were less concentrated and were prepared from magnesium sulphate plasma instead of oxalated plasma.

The difference between the two bloods in respect to their content in thromboplastin was brought out also when a fibrinogen solution was prepared from equal quantities of each by precipitation with ammonium sulphate. In each case three precipitations were used and the final solution of fibrinogen was tested for its thromboplastin content upon hemophilic blood. The fibrinogen solution from normal plasma caused clotting of hemophilic blood in a few minutes while that from hemophilic plasma had little or no action. In one such experiment, for example, the control with saline clotted in fifty-seven minutes, the fibrinogen solution from normal plasma caused clotting in fourteen minutes and that



from the hemophilic plasma in forty-eight minutes

Saline solutions of the plasma thromboplastin obtained by the method described always contain protein, but the protein is not concerned in, or at least, is not essential to the clotting reaction, since solutions of thromboplastin showing its characteristic reaction on hemophilic blood may be obtained free from protein. The simplest method for this purpose is extraction with glycerol. The precipitate obtained from diluted plasma by the addition of acid, after washing with distilled water to remove adherent plasma, is stirred in glycerol, allowed to extract for twenty-four hours in the ice box and then filtered. The extract is free from protein as far as can be determined by the ninhydrin and biuret reactions. In testing its effect on hemophilic blood it was usually diluted with two volumes of a 1.5 per cent solution of sodium chloride and its effect compared with that of a control solution consisting of one part glycerol and two parts 1.5 per cent solution of sodium chloride. Glycerol itself in this dilution accelerates slightly the time of clotting, compared with an equal volume of physiological saline, but far less than the glycerol extract. A typical result is, as follows: Hemophilic blood 0.5 cc + glycerol extract of thromboplastin 0.3 cc, clot in 14 minutes, hemophilic blood 0.5 cc + glycerol-saline solution 0.3 cc, clot in 51 minutes. The solubility of the coagulin in glycerol must be small since it does not seem possible to get concentrations that have as strong an action as the saline extracts. I have obtained plasma thromboplastin free from protein also by precipitating the protein in the extracts with petroleum ether. The method is uncertain and is successful only when the amount of contaminating protein is small. I have referred to the fact that when fibrinogen is prepared from plasma by the ammonium sulphate method it always contains some thromboplastin. If the fibrinogen is removed by heating to  $56^{\circ}$  the thromboplastin is left in solution together with a small amount of an unknown protein which undergoes heat coagulation at  $75^{\circ}$  to  $80^{\circ}\text{C}$ . If a solution of this kind, from which the fibrinogen has been removed, is shaken with two volumes of petroleum ether a gelatinous precipitate forms. If this is removed and dried and extracted with physiological saline, a solution is obtained which is protein free but which accelerates distinctly the clotting of hemophilic blood. The petroleum ether used contains none of the active substance.

Blood plasma contains only small amounts of thromboplastin and it did not seem feasible to obtain it protein-free from this source in suffi-

cient amounts to make any progress in determining its chemical nature I have therefore turned to a study of the tissue thromboplastin. It has long been known that the tissues contain a thromboplastic substance which accelerates the clotting of blood and a number of workers have called attention to the fact that this substance is found in especially high concentration in the lungs. Specimens of hemophilic blood which require one or more hours before coagulation begins will set to a firm clot in less than a minute when mixed with a small amount of lung extract. Numerous attempts have been made to utilize extracts of the lungs or other tissues in the control of hemophilia or as a hemostatic agent in general. Preparations of this kind have come upon the market under trade names such as the coagulen of Kocher-Fonio, the eluden of Fischl, fibrinogen-Merrell of Mills, thromboplastin. The therapeutic value of these agents used intravenously or intramuscularly has been reviewed critically by Gold.<sup>1</sup> The results from their use in the hands of different observers seem to be contradictory and are not unattended by danger from protein reactions or intravascular clotting. Nevertheless, there is no question that in the tissues and especially in the lung tissue there is a substance which has a remarkable effect in accelerating the clotting of hemophilic blood *in vitro*. It would seem that we should be able to obtain this substance in pure form and to utilize it in controlling hemophilic bleeding.

The active substance as usually obtained is associated or combined with protein but by a modification of the method of extraction I have succeeded in obtaining it in a protein-free condition and in a form suitable for chemical examination. The details of the method will be given in a later publication. The essential point is that the acid precipitate of the aqueous extracts of the lungs, after purification by repeated precipitations is extracted with distilled water in large volume and this dilute solution or suspension is precipitated by the addition of acid to a pH of about 4. The precipitate is obtained by centrifuging and is further purified by extraction with chloroform. The yield is small, about 10 to 15 mgm per gram of dried lung tissue, but the method no doubt can be improved in this respect. The material obtained is soluble in slightly alkaline aqueous or saline solutions and shows great activity in accelerating the clotting of hemophilic blood, an activity of the same order as that of extracts of lung tissue. It shows the following properties. It is apparently insoluble in chloroform, ether and benzol and its activity is de-

stroyed by the action of alcohol or acetone. It does not contain a carbohydrate group. It gives positive reactions for phosphorus and nitrogen. Fused with acid potassium sulphate it gives reactions for glycerol and one may assume that it contains a glycerophosphate group. It is interesting to note in this connection that Freund<sup>22</sup> in 1910, in a report made to the International Physiological Congress, stated that by hydrolysis of lecithin he obtained a substance that he believed to be a calcium diolein glycerophosphate which showed marked thromboplastic activity. It is possible of course that the material as I have isolated it, may contain substances other than the thromboplastin. This must be determined by further work.

The thromboplastic material of the tissues has been investigated by many observers. As is well known two kinds of extracts have been made, aqueous or saline extracts which yield a very active thermolabile compound, containing protein, the thrombokinas of Morawitz, and alcohol-ether extracts which are less effective and in which the active constituent is believed to be the phospholipid, cephalin. Extracts of the latter kind yield the zymoplastic substance of Schmidt and the cytozyme of Boidet. It has been suggested by Howell, Mills and others that cephalin constitutes the active component in water extracts also, on the theory that in the tissues it is in combination with protein and in this form exhibits thermolability as well as greater potency. The work here reported, however, does not support this view. It indicates on the contrary that the active substance in aqueous extracts, of the lung tissue, at least, is not a known phospholipid, although it may possibly be a derivative product.

In the lungs the thromboplastin is associated apparently with a nucleoprotein and in blood plasma mainly with the globulins. While this association may modify its reactions it does not seem to enhance its thromboplastic activity since the protein-free thromboplastin is still remarkably potent.

As far as blood is concerned we may conclude that one real difference between normal and hemophilic blood is that the latter contains less thromboplastin in its plasma. There may be other differences but they have not been discovered. It would seem permissible to assume that this deficiency is sufficient to explain the prolonged clotting time of hemophilic blood, since clotting takes place normally when the deficiency is removed by the addition of thromboplastin extracts, *in vitro*, or *in vivo*, by the transfusion of the plasma of normal blood or the intravascular in-



inherited defect in hemophilia lies in this abnormality in composition of the plasma. This conclusion may be correct but in one respect their experiment seems to me to be unsatisfactory. For a normal plasma they used a decalcified blood in which coagulation was induced by recalcification. What changes are caused by decalcification and recalcification are not fully known but plasma so treated can scarcely be regarded as an entirely normal environment for platelets. For the point at issue it would be a crucial experiment if uninjured hemophilic platelets could be transferred to a platelet-free normal human plasma without employing any decalcifying or anticoagulating agent. This has not been done and it is difficult to see how it could be accomplished. The reverse experiment of transferring normal platelets to a platelet-free hemophilic plasma is more feasible and has been attempted by Fonio.<sup>25</sup> In his experiments hemophilic blood was received into paraffined centrifugal tubes packed in ice which were then centrifuged at high speed and at a low temperature. In this way he obtained a platelet-free hemophilic plasma which at room temperature clotted very slowly in from four to eight hours. If to this plasma he added suspensions of washed platelets from normal and from hemophilic blood the clotting was greatly accelerated but much more in the case of the normal than in that of the hemophilic platelets although the final result was the same for both. Here apparently under the same conditions the platelets behaved differently, those from hemophilic blood showing greater stability. There was nothing in the hemophilic plasma to retard the breaking down of the normal platelets. From this point of view the inherited defect in hemophilia would lie in the structure of the platelets or of the megakaryocytes from which they are derived. In a former publication I have advocated a similar view, but it must be admitted that such a theory is at variance with the conclusion to be drawn from the newer work that I have been describing. The point is this. When blood is transfused into a hemophilic patient, or globulin substance is injected, the thromboplastin content of his plasma is increased but not enough to cause intravascular clotting. We may assume that in this respect the hemophilic plasma is brought to an approximately normal condition. If now this blood is withdrawn from the circulation it clots normally. The hemophilic platelets presumably agglutinate and break down in what we may consider the normal time, that is to say, when the plasma is right they exhibit no abnormal stability.

The part taken by the thromboplastic substance of the blood in

clotting is a difficult and controversial subject which I shall not attempt to discuss at length. It may be said that thromboplastin when present in sufficient concentration causes coagulation of the plasma without participation by the platelets. Platelet-free hemophilic plasma obtained by centrifuging the blood at high speed in paraffined tubes clots solidly in one to two minutes on the addition of a solution of purified thromboplastin prepared from lung tissue and it has long been known that rapid intravenous injections of tissue extracts cause almost immediate intravascular clotting. It would seem therefore that in the circulating blood the content of thromboplastin must be below the concentration required to induce prompt clotting. When blood is shed or withdrawn, the content of thromboplastin is increased with some suddenness by the mass disintegration of the platelets to a concentration sufficient to cause clotting within a few minutes the actual time varying with conditions such as temperature or contact with a foreign surface. A point of interest is whether or not the thromboplastin has any direct influence upon the agglutination and breaking down of the platelets. I have no conclusive data upon this point but I am inclined to believe that thromboplastin does not affect the platelets directly although it may do so indirectly by setting up certain chemical changes in the plasma. Platelets when removed from their normal environment by centrifuging and washing exhibit a marked rigidity in structure. In saline or even aqueous suspensions they retain their shape do not agglutinate and show no tendency to break down upon contact with glass or other foreign surface. Addition of solutions of thromboplastin to such suspensions does not seem to affect the platelets in any way. Yet in shed blood, platelets do agglutinate and disintegrate quickly, and when the concentration of thromboplastin is subnormal, as in the case of hemophilic blood, the process is markedly delayed, indicating that the thromboplastin is concerned in some way in the changes undergone by the platelets. These contrary indications are difficult to reconcile, but it is clear, I think, that the primary function of the thromboplastin is to participate in the activation of prothrombin to thrombin. In shed blood, both physical and chemical factors may accelerate this reaction and thereby alter conditions so as to affect the platelets. For example, platelet-free or platelet-poor hemophilic blood in mass in a glass container clots very slowly and much more slowly if the walls of the container are paraffined. But if a sample of this plasma is placed in a counting chamber and observed under the microscope it will be found

that clotting begins in a few, five to ten, minutes. Needles of fibrin are deposited in the plasma quite independent of any platelets that may be present and they increase rapidly in number until a meshwork of fibrin is formed. The greater physical contact with the glass surface in this case seems in itself to accelerate the chemical changes leading to the formation of thrombin, and it is possible that some product of this reaction, in which thromboplastin is concerned, may affect the integrity of the platelets, in addition to the well known influence of contact with a foreign surface. However these are speculations which serve mainly to emphasize some of the problems that need further study.

In conclusion something may be said in regard to the therapeutic treatment of hemophilia. What we can hope for is some method of controlling promptly internal and external hemorrhages, for there is little reason to believe that an hereditary defect of this kind can be permanently cured by treatment. External capillary hemorrhages from small wounds or abrasions of the skin are not usually serious, since the admixture of the tissue juices is sufficient to ensure clotting. In wounds of larger vessels the ordinary surgical methods of closing the wound may be supplemented by transfusion and by the application of freshly prepared tissue extracts. I have lately found that glycerine extracts of dried lung give an unusually potent preparation that might be used for such a purpose. It has the advantage that it retains its activity for a long period if kept in the ice box. The more serious problem is the control of the internal hemorrhages. The customary method used for this purpose is the transfusion of normal blood. In the majority of cases reported this method has proved to be efficacious. The curves given by Patek and Stetson<sup>18</sup> show that after such transfusions the clotting time of the hemophilic blood falls quickly toward or to the normal and may remain at this level for a number of hours or for a day or two. It then returns somewhat rapidly to its former condition. Since a similar effect is produced when blood plasma alone is used it may be assumed that the result is due not to the corpuscles but to some constituent in solution in the plasma. Normal plasma, as we have seen, differs from hemophilic plasma, so far as our positive knowledge goes, only in having more thromboplastin, and we may conclude therefore that the good effect of the transfusion is due to the fact that it increases the concentration of thromboplastin in the hemophilic blood. This conclusion is supported by the direct experiments of Patek and Stetson<sup>18</sup> and of Pohle and Taylor<sup>19</sup> which

show that intravenous injection of their "globulin-substance" causes a shortening of the coagulation time comparable to that produced by blood transfusions. It may be that there are other factors or conditions involved which influence or modify the effect of the thromboplastin. Some facts, at least, are known which indicate that the time of coagulation does not always vary directly with the concentration of thromboplastin in the blood. It is stated for instance by Leissly<sup>12</sup> that transfusions of as little as 10 to 20 cc. of normal blood suffice to bring the coagulation time of hemophilic blood within normal limits. Patch and Stetson<sup>13</sup> also report that transfusions of 30 to 40 cc. of citrated blood may have the same effect as much larger amounts, and Pohle and Taylor<sup>14</sup> found that in a patient subjected to repeated injections of globulin substance, at six hour intervals a refractory state may develop during which the coagulation time seems not to be affected by an increase in the substance in the plasma. However this may be, we have the practical result that the coagulation time of hemophilic blood may be restored to normal by injection of solutions of thromboplastin. Experience must determine whether this substance in purified form may be used as a safe substance for blood transfusion.

Many other methods of controlling hemophilic bleeding have been suggested but the claims made for their efficacy have not in most cases been confirmed by subsequent experience. It is not possible to refer to all of these methods but a word or two may be said about some that have been recently proposed. Birch<sup>26</sup> proceeding upon the theory that the hemophilic is lacking in the female sex hormone has treated cases successfully with ovarian extracts and estrone injections. Her results have been confirmed by some observers and denied by others. I have not myself been able to detect any positive effect of injections of theelin upon the coagulation time of hemophilic blood. The careful study of seven cases by Stetson and his co-workers<sup>13</sup> seems to demonstrate conclusively that the feeding or injection of ovarian extracts and estrogenic preparations has no distinctly beneficial effect upon hemophilic bleeding or the coagulation time of the blood.

Timperley, Naisch and Clark<sup>27</sup> report upon a new material which they obtain by incubating a mixture of egg white and potassium bromide. The chemical nature of the active substance derived from this mixture was not known, but its use intravenously gave most interesting results. There was no reaction, the coagulation time of the blood was reduced



to normal and if the injections were made during an attack they brought relief to the patient. Unfortunately these results have not met independent confirmation from other workers, and the authors themselves have not so far been able to devise a reliable method for obtaining the effective substance.

Lawson and Graybeal<sup>28</sup> report good results from simply bleeding the patient. Blood in amounts from 170 cc to 500 cc was withdrawn by syringe at the time of attacks with the result that the patient showed marked improvement and disappearance of symptoms. In one case bleeding was done periodically over a stretch of seven years, 500 cc being withdrawn every six to eight weeks. They report that during this period there was a cessation of serious attacks which before had been frequent. The authors do not state the effect of these bleedings upon the coagulation time. It was a former belief, based upon Sahli's<sup>6</sup> work, that severe hemorrhage in the hemophiliac causes a reaction of some kind that affects the coagulation of the blood, bringing it back to normal, thus affording a mechanism for automatically controlling the hemorrhage, but later observers (Schloessmann<sup>3</sup>) have not been able to confirm this result.

Many attempts have been made also to control the coagulation time in hemophilia through the diet or by extracts administered through the mouth. These attempts so far as I know have been uniformly unsuccessful. Some years ago I tested a number of these methods upon one of my cases. The series consisted of Natena tablets, Llopis, a mixture of vitamins A, B, C, D, with calcium phosphate and milk sugar, ceanothyn, the mixed alkaloids of *Ceanothus Americanus*, cephalin, a crude extract from brain in aqueous suspension, Howell, a liver and grapefruit diet, Pickering, spleen and bone-marrow extracts, Leake, ovarian extracts and theelin, Birch, placental extracts, Eley, extracts of fresh lung, extracts of dried lung, brewers' yeast, cod liver oil, hemostyl, serum hemopoietique, Roussel, rivanol, hexylresorcinol, carbon tetrachloride, sodium bicarbonate, alkalosis, ammonium chloride, acidosis, fasting for a period of forty-eight hours. None of these substances had a definite effect. At times there might appear to be a shortening of coagulation time, never a return to normal although a considerable diminution, but on repetition uniform results could not be obtained, the effect was inconstant. I was forced to conclude that such variations as occurred were due to spontaneous changes in the coagulation of the blood or to small differences in the technique

of sampling. During the present year I have tried the effect of administering by mouth solutions of purified thromboplastin, obtained from lung which *in vitro* caused hemophilic blood to clot within one or two minutes but the results were entirely negative. It would seem to be impossible to affect the coagulation time of the blood in a definite way by absorption from the alimentary canal. For the control of hemophilic hemorrhages we must rely at present chiefly upon transfusions but there is a prospect that further study of the chemistry and reactions of thromboplastin may provide a more convenient treatment in which the dosage may be regulated to meet the severity of the symptoms.

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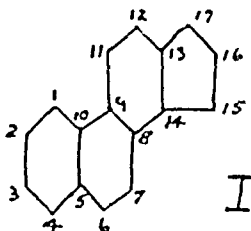
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# SOME ASPECTS OF THE INTERMEDIARY METABOLISM OF THE STEROID HORMONES\*

*Harvey Lecture October 20 1938*

GUY FREDERIC MARRIAN

I must begin by reminding you that the term "steroid" has now come into general use following the suggestion of Callow and Young<sup>1</sup> is a group name for all substances containing the cyclopentanophenanthrene carbon skeleton (I)



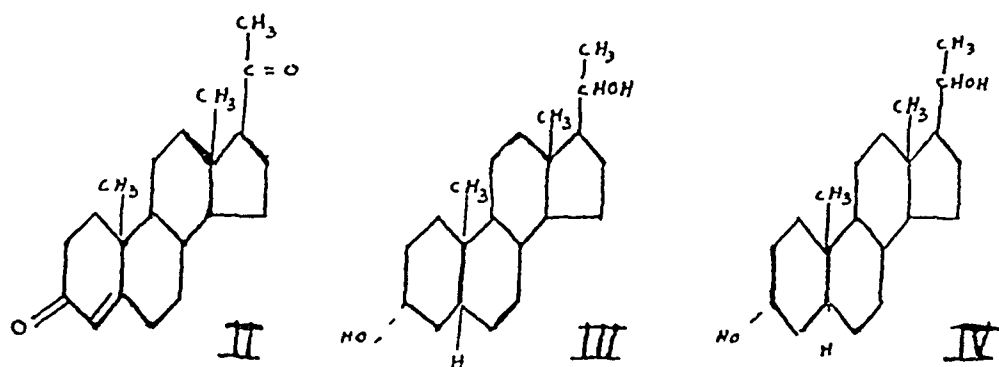
Among the large number of interesting naturally occurring compounds which possess this carbon skeleton are four groups of hormones the estrogens elaborated by the ovary and also possibly by the placenta, the androgens of the testis the progestational hormone of the corpus luteum and the "life-maintaining" hormone or hormones of the adrenal cortex. These hormones may therefore be conveniently called "steroid hormones."

During the past ten years interest in these hormones has been largely centered round the problems of their exact chemical constitutions and of their respective physiological functions in the animal body. We are now, I believe, at the beginning of a new phase in research upon these steroid hormones, a more purely biochemical phase, arising out of and made possible by the achievements of the organic chemists and physiologists during the past decade, the ultimate object of which is the elucidation of the chemical mechanisms involved when these hormones produce their physiological effects in the organs and tissues upon which they act. Already in a number of different laboratories, studies have been made upon the

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nature of the chemical reactions involved when certain of these hormones are inactivated in or eliminated from the body, and speculating upon their possible modes of origin and interconversion is rapidly becoming the fashionable biochemical pastime

So rapidly has this field expanded during the past few years that the task of reviewing it critically and comprehensively is an impossible one in the short time at my disposal. I must therefore regretfully limit myself mainly to an account of some of the problems in which I and my colleagues are at present interested, mentioning the results and theories of others only when they are strictly relevant



It will be convenient to begin by mentioning some of the well established facts about metabolic changes undergone by the hormone of the corpus luteum, progesterone (II)

It is a point of some historical interest that a metabolic reduction product of progesterone had been isolated and chemically characterized five years before the hormone itself was isolated in a crystalline form. This compound, pregnanediol (III), was first isolated by myself<sup>2</sup> in 1929 in a slightly impure state from human pregnancy urine. A few months afterwards it was independently isolated by Laqueur and his co-workers<sup>3</sup> and by Butenandt<sup>4</sup> from the same source. The latter was soon able to establish the structural relationship of this compound to the bile acids with complete certainty.<sup>5</sup>

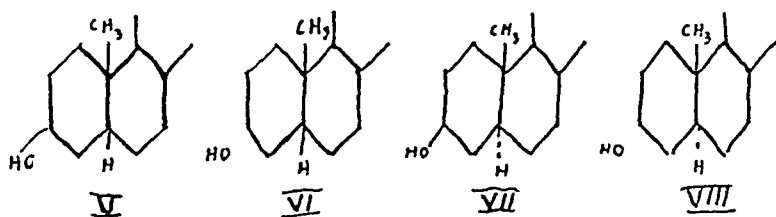
The true significance of the presence of this steroid in pregnancy urine could not at that time be appreciated. However, as soon as the constitution of progesterone had been established in 1934, it was immediately seen that pregnanediol might be a metabolic product of the hormone, formed by the reduction of its two ketonic groups and of its double linkage. The discovery by Hartmann and Locher<sup>6</sup> in human pregnancy

urine of a stereoisomer of pregnanediol—allopregnanediol (IV') which differed from the former in its steric configuration at C<sub>13</sub>—provided support for this view since the presence of both C<sub>13</sub> stereoisomers in urine implied that both must have been formed in the body by the addition of hydrogen to a double-linked (and therefore non-symmetric) C<sub>13</sub> of a common precursor. Conclusive proof that pregnanediol is indeed a metabolic product of progesterone has been recently put forward by Venning and Browne.<sup>10</sup> They were able to show in the first place that pregnanediol is present in human pregnancy urine in combination with glucuronic acid. This observation, interesting enough in itself, assumed great practical importance when it was found that the solubilities of the sodium salt of this pregnanediol glucuronic acid conjugate were such that it could be quantitatively determined in pregnancy urine with a fair degree of accuracy by a relatively simple procedure. Using this method of determination they were successful in demonstrating an increase in pregnanediol excretion in a non-pregnant woman following the administration of progesterone.<sup>11</sup> We are therefore fully justified in recognizing pregnanediol as an end product of the metabolism of progesterone and it follows that the same may be said of allopregnanediol. As far as I am aware there are no reliable figures in the literature to indicate the relative amounts of these two end-products of progesterone metabolism which are excreted in the urine. My own experience with pregnancy urine extracts, however, leaves me in no doubt whatsoever that the reduction of progesterone in the body leads to the formation of much more pregnanediol than allopregnanediol. As we shall see later, it is possible that this fact may not be devoid of biological significance.

As might be expected, pregnanediol and allopregnanediol are not the only simple reduction products formed from progesterone in the body. Many partly reduced intermediates are theoretically possible, and since the addition of hydrogen to the three reducible groups of progesterone involves the formation of three new asymmetric carbon atoms, a very large number of products might result from the simple reduction of the hormone. Several of these have indeed been isolated from human pregnancy urine by Marker and his collaborators.<sup>10, 11, 12</sup>

Before proceeding any further, I must digress for a moment in order to explain the particular system of nomenclature which I intend to use when I am referring to stereoisomers in this series of compounds. If the C<sub>13</sub> hydroxyl group in a particular compound has the same steric config-

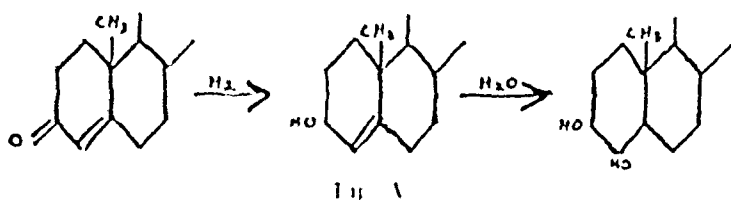
uration as that of the hydroxyl group in cholesterol, which is assumed to be *cis* to the C<sub>10</sub> angular methyl group, it is designated by the prefix  $\beta$ -. Thus the partial formulae (V) and (VII) are of 3 $\beta$ -hydroxy compounds. Such compounds are precipitated by digitonin. When the C<sub>3</sub> hydroxyl group has the epimeric configuration as in the partial formulae (VI) and (VIII), the prefix  $\alpha$ - is used. Such compounds are not as a general rule precipitated by digitonin. The prefix *allo*- is, as I have already implied, used to designate the steric configuration at C<sub>7</sub>. Thus in accordance with this system of nomenclature, the compounds which I have been somewhat loosely referring to as pregnanediol and allopregnanediol, and which are of types (VI) and (VIII) respectively, should be called pregnane-3( $\alpha$ ), 20-diol and allopregnanane-3( $\alpha$ ), 20-diol.



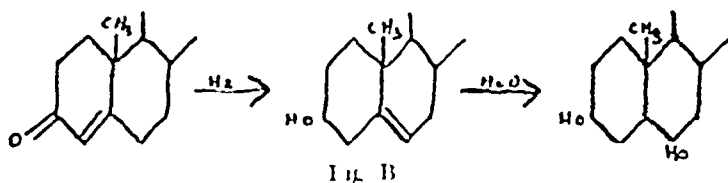
Some years ago, before the relationship between pregnanediol and progesterone had been discovered, Dr Haslewood and myself were attempting to show the presence of the former substance in the urine of pregnant mares. We failed to do so, but we succeeded in isolating another interesting substance which we suspected might be closely related to pregnanediol.<sup>13</sup> This compound gave analyses in close agreement with those required for a triol of the formula C<sub>21</sub>H<sub>33</sub>(OH)<sub>3</sub>, but since we were unable to make any molecular weight determinations we were unable to go further than stating that it had the empirical formula (C<sub>7</sub>H<sub>11</sub>OH)<sub>n</sub>.

Within the last year Marker and his associates<sup>14</sup> have also isolated this compound from the urine of pregnant mares, and more recently<sup>15</sup> have published results which they claim prove that this compound is pregnane-3( $\alpha$ ), 4( $\beta$ ), 20-triol. They suggest that this compound is formed from progesterone by the reduction of both ketonic groups and the addition of the elements of water to the double linkage in the manner shown in Fig. A.

This view of the structure of the compound is one with which I cannot agree. Dr Odell and I<sup>16</sup> have been working on the constitution of this compound for the last three years. Our evidence on its structure is not



yet complete but the data which we have so far obtained is absolutely irreconcilable with the conclusion of Marker *et al*. If the compound is indeed a steroid with three hydroxyl groups, two of which are at positions 3 and 20—and of this we ourselves have no proof at present—then our evidence indicates that it is very probably a pregnane or allopregnane-3( $\alpha$ ), 6, 20-triol. The formation of such a compound from progesterone could be explained on the reasonable supposition that after the reduction of the C<sub>3</sub> ketonic group and before the addition of the elements of water, the double linkage shifts from the 4-5 to the 5-6 positions as shown in Fig. B.



At the present time the biochemical significance of the presence of this compound in the urine of pregnant mares is not at all clear. At first we were inclined to believe that it represented the main end-product of progesterone metabolism in the mare, occupying a position in the metabolic scheme analogous to that occupied by pregnanediol in the human. However, since it has recently been shown by Marker *et al*<sup>17</sup> that pregnant mares' urine contains as much pregnanediol and allopregnanediol as does human pregnancy urine, this view must clearly be abandoned.

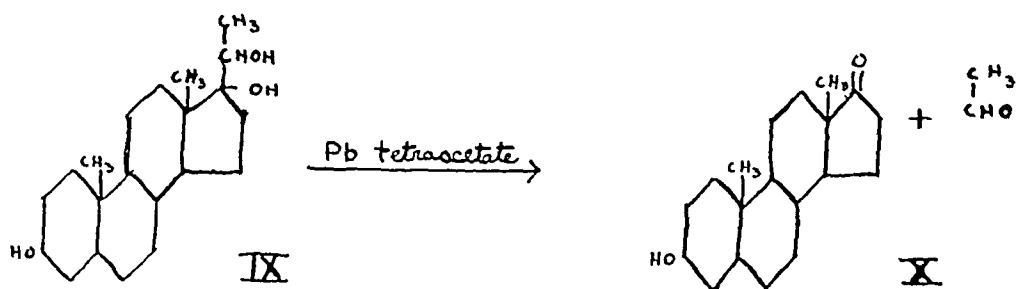
Although the position of this interesting triol in steroid metabolism is still obscure, there are no doubts in my own mind concerning the importance of its position in our own work on steroids, since it has been responsible for the initiation of a new line of research which promises to lead us to a real understanding of certain phases of steroid metabolism. Our isolation of the triol from mares' urine, led me some years ago to look for it in human pregnancy urine. I failed to find it, but I was able to isolate another new compound, which for brevity I will refer to as *x*. We are at present



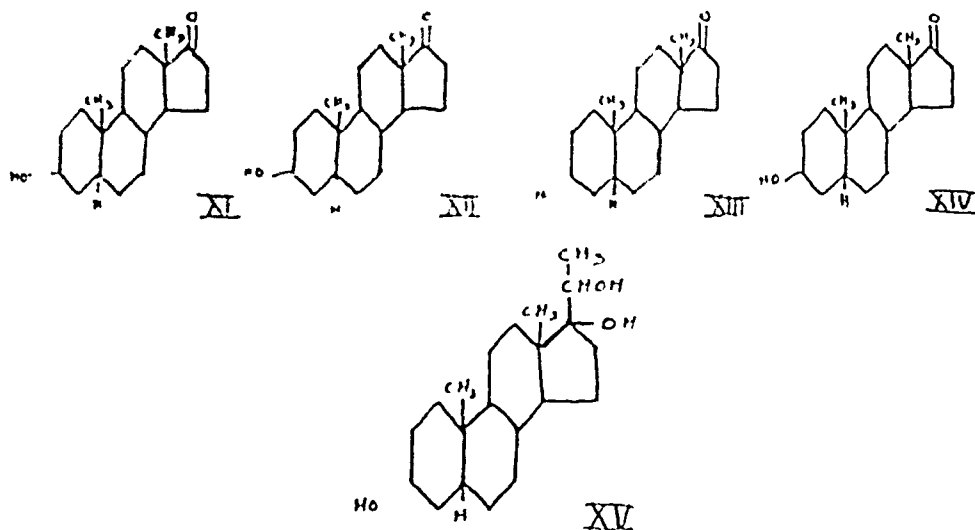
working on the constitution of 1, but so far we have not progressed far enough to permit us even to hazard a guess concerning its structure, and therefore I am unable to make any speculations concerning its role, if any, in steroid metabolism. However, at one time I had the idea that 1 might be a metabolic product of certain of the adrenal steroids, and I therefore suggested to Dr. Butler that we might search for it in urine specimens obtained from individuals with hyperplastic adrenals. Mr. L. R. Broster of the Charing Cross Hospital, London, very kindly came to our assistance, and sent us several concentrates of urine obtained from women with marked symptoms of adrenal virilism and upon whom he subsequently operated. We were completely unsuccessful in isolating 1 from these urines, and I might add that we have now no grounds for believing that 1 is derived from the adrenal steroids as I had originally supposed. However, while we were looking for it, we found another new compound which almost certainly is an adrenal product, since we have never encountered it in any urines except those obtained from adrenal virilism cases.<sup>18</sup>

This new compound proved to be a saturated triol of the formula  $C_{21}H_{33}(OH)_3$ —isomeric with but different from the triol in pregnant mares' urine. The elucidation of its constitution proved to be a surprisingly simple matter. We found that two of the three hydroxyl groups were easily esterifiable, whereas the third was not—a fact which suggested that the latter might be tertiary. We next indulged in some guessing. On the assumption that it was a steroid of the pregnane or allopregnane type with hydroxyl groups at positions  $C_3$  and  $C_{20}$ , we guessed that the third hydroxyl group might be at  $C_{17}$ , by analogy with certain of the adrenal steroids, thus arriving at the hypothetical formula shown below (IX).

Such a compound should be capable of being oxidized by lead tetra-



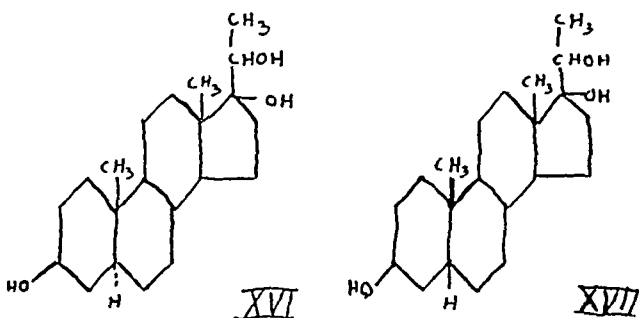
acetate to yield acetaldehyde and a hydroxyketone of the formula  $C_{19}H_{26}O_2$  (X). Accordingly we attempted to oxidize our compound with this reagent. We found that it was oxidized and in the products we identified acetaldehyde and a hydroxyketone which analyzed for  $C_{19}H_{26}O_2$ . It was apparent that if our original guess was correct the latter must be androsterone (XI), isoandrosterone (XII), 3( $\alpha$ )-hydroxy androcholane-17-one (XIII) or 3( $\beta$ )-hydroxy androcholane-17-one (XIV). It proved to be identical with 3( $\alpha$ )-hydroxy androcholane-17-one. Consequently we had proved that the triol was pregnane-3( $\alpha$ ),17,20-triol (XV).



During the progress of this work we encountered in certain of the urine fractions small amounts of other crystalline substances. We therefore decided to attempt to work up much larger quantities of urine from adrenal virilism cases in order to obtain these other compounds in amounts sufficiently large for identification. Mr. Broster once again came to our assistance and sent us the concentrate from forty-five liters of urine collected from a female patient with adrenal hyperplasia and definite symptoms of virilism. The extract from this concentrate was systematically fractionated and yielded, as we had anticipated, several crystalline compounds, some of which we were able to identify with certainty.<sup>10</sup> The non-ketonic fraction yielded the same pregnane-3( $\alpha$ ),17,20-triol, which we had previously isolated from the earlier urine specimens, while from the ketonic fraction we obtained two hydroxy ketones of the formula  $C_{19}H_{26}O_2$ . One of these was easily identified as isoandrosterone (XII) while the other proved to be 3( $\alpha$ )-hydroxy androcholane-17-one (XIII).

Both of these substances were prepared by Ruzicka<sup>20</sup> from cholesterol in the course of his classical work on the constitution of pseudo-synthesis of androsterone. Neither of these compounds, however, had previously been isolated directly from any natural source. The identification of isoandrosterone is of some interest in connection with the etiology of adrenal virilism, since it possesses weak, but quite definite androgenic potency.

The presence in the same urine specimen of pregnane-3( $\alpha$ ),17,20-triol and of 3( $\alpha$ )-hydroxyaetiocholan-17-one, the substance to which the former gives rise by oxidation with lead tetra-acetate, struck us as being very significant. It seemed probable to us that an oxidation similar to that which can be effected in the laboratory with lead tetra-acetate must have occurred in the body. Following this line of reasoning further, we decided that probably the isoandrosterone had arisen in a similar manner by an oxidative removal of the side chain of allopregnane-3( $\beta$ ),17,20-triol (XVI), which bears the same structural relationship to it as does pregnane-3( $\alpha$ ),17,20-triol to 3( $\alpha$ )-hydroxyaetiocholan-17-one.

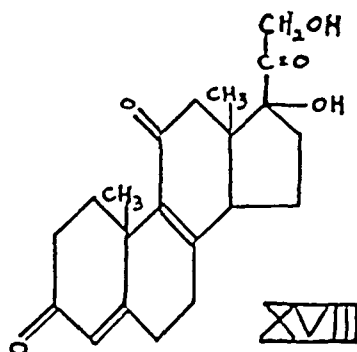


We accordingly conducted a search in our urine extracts for allopregnane-3( $\beta$ ),17,20-triol. We have so far failed to find it, but Reichstein<sup>21</sup> has recently reported the isolation from adreno-cortical extracts of two isomeric allopregnane-3( $\beta$ ),17,20-triols which must differ from one another in their steric configurations at C<sub>17</sub> and/or C<sub>20</sub>. Either of these could therefore give rise to isoandrosterone by a side-chain oxidation of the type that we suggest takes place in the body.

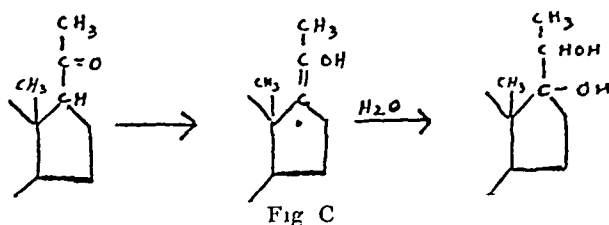
While we were conducting our abortive search for allopregnane-3( $\beta$ ),17,20-triol in urine, we isolated another triol. We had insufficient data for complete identification, but our evidence, such as it is, very strongly suggests that it is pregnane-3( $\beta$ ),17,20-triol (XVII). If our theory of side-chain oxidation is correct, then this triol should give rise to

3( $\beta$ )-hydroxy androcholane-17-one (XIV) in the body. We have not so far been able to isolate this hydroxyketone from adrenal virilism urine. If we could do so, the evidence in favor of our theory of side-chain oxidation would be extremely convincing. As it is, the evidence is sufficiently strong in my opinion to justify its provisional acceptance as a basis for further work and speculation. It may be mentioned at this point that if our new triol is indeed pregnane-3, 17, 20-triol, its presence in urine will not be in line with the recent prediction of Marker<sup>12</sup> that saturated 3( $\beta$ )-hydroxy steroids of the coprostane series will not be found in urine or tissues.

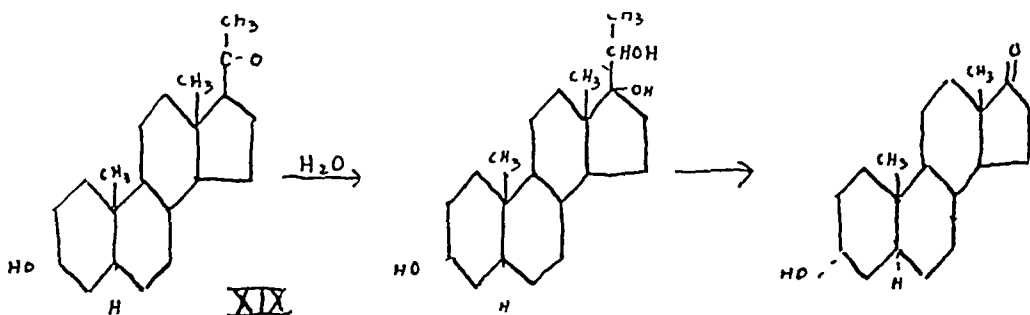
I must next discuss the problem of the mode of origin of these pregnane- and allopregnan-3, 17, 20-triols. Marker<sup>12</sup> has recently put forward the suggestion that the fundamental steroid from which all the adrenal steroids, the estrogenic and androgenic hormones are formed is the so far unknown  $\Delta^4$ -pregnadiene-17, 21-diol-3, 11, 20-trione (XVIII) and which he suggests may be identical with the true adreno-cortical hormone.



According to his theory, therefore, all these steroids are formed from a precursor which already possesses a  $C_{17}$  tertiary hydroxyl group. Dr. Butler and I hold a somewhat different view. We suggest that the steroids with  $C_{17}$  tertiary hydroxyl groups are secondary products which are formed by the addition of the elements of water to the double linkage of an enolized  $C_{20}$  ketonic steroid in the manner shown in Fig. C.



If this represents the true state of affairs and if our theory of side-chain oxidation is correct, then steroids with the allopregnane carbon skeleton, with  $C_3$  hydroxyl or ketonic groups, and with  $C_{20}$  ketonic side chains attached to  $C_{17}$ , might be expected to have androgenic properties, since by the addition of water to the side-chain in the manner depicted above, and by subsequent oxidation between the so-formed  $C_{17}$  and  $C_{20}$  hydroxyl groups, androgenic compounds might be formed in the body. At the moment this is almost pure speculation supported by no experimental evidence of our own. Marker *et al*<sup>10, 23</sup> have, however, made an observation which could be explained on the basis of our speculative theories, and which therefore provides them with some measure of experimental backing. From human pregnancy urine these workers isolated allopregnane-3( $\alpha$ )- $\alpha$ - $\alpha$ - $\alpha$ -one (XIX), one of the partial reduction products of progesterone, and they made the astonishing claim that it possesses powerful androgenic properties. We would suggest that the androgenic potency of this compound might be explained by supposing that it adds on the elements of water to the side-chain and is then oxidized with the formation of androsterone, according to the scheme shown below.



I have already pointed out that in reducing the double bond of progesterone the human body seems to have a preference for forming compounds of the pregnane rather than of the allopregnane type, as indicated by the fact that the pregnant woman excretes much more pregnanediol than allopregnanediol. This fact appeared to us to be somewhat significant in the light of our speculative theories, since the formation of an excess of reduction products of the allopregnane type might give rise to unwanted and harmful androgens by the series of reactions which we suggest may occur in the body.

In order to consider further the nature of the precursor or precursors

from which these isomeric triols arise, it will be convenient to make a list of the latter

- (a) pregnane-3( $\alpha$ ),17,20-triol from urine,
- (b) pregnane-3( $\beta$ ),17,20-triol from urine,
- (c) two allopregnane-( $\beta$ ),17,20-triols from adrenals

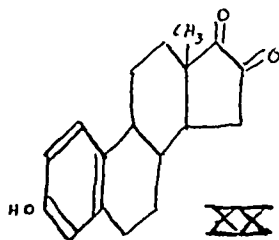
Now (a) differs from (b) and (c) in the configuration at the asymmetric  $C_3$ . It is therefore justifiable to assume that both  $C_3$  stereoisomeric types have arisen from a common precursor with no asymmetry at  $C_3$ —that is to say probably from a compound with a  $C_3$  ketonic group. Similarly (a) and (b) differ from (c) in the configuration at the asymmetric  $C_5$ . It therefore follows that both  $C_5$  stereoisomeric types probably have arisen from a precursor with a double linkage at  $C_5$ . We are now in a position to attempt to identify this hypothetical precursor. Since it probably has ketonic groups at  $C_{20}$  and  $C_3$  and probably has a doubly-linked  $C_5$ , it seems likely that it may be progesterone itself. Dr. Butler and I therefore believe that the various isomeric triols that are found in the urines of adrenal virilism patients and in the adrenal gland, are formed from progesterone in the adrenal cortex.

In support of our belief there is now a considerable weight of evidence that indicates that progesterone is manufactured in large amounts in the adrenal gland. In the first place Dr. Butler and I have observed that women with adrenal virilism symptoms excrete abnormally large amounts of pregnanediol, which, as has already been seen, is the chief end product of progesterone metabolism in women. Secondly, Callow and Parkes<sup>24</sup> have shown that extracts of the adrenals of certain species are highly potent in inducing progestational proliferation of the uterus of experimental animals. Finally, a few weeks ago, Beall and Reichstein<sup>25</sup> independently isolated pure progesterone itself from adrenal extracts. There can therefore be little doubt, I feel, that our contention that progesterone occupies a key position in steroid metabolism in the adrenal gland is substantially correct.

Before I conclude, I wish to spend a short time describing some work along somewhat different lines which Mr. Darrach and I have been carrying out during the past two years and which promises eventually to throw much light on the intermediary metabolism of the estrogenic hormones. The original problem which Mr. Darrach and I set out to study was the purely academic one of the chemical mechanism of the well known Kober color reaction for estrogens. It will be recalled that this

color reaction consists of the production of a red color when an estrogen is heated with concentrated sulphuric acid or phenolsulphonic acid and the mixture subsequently diluted with water

We found in the first place that the red color in the reaction mixture could be discharged by neutralizing the solution with sodium bicarbonate, and that restoration of the original red color could be achieved by reacidification, the color change occurring at a pH of somewhat less than 10. These facts suggested to us that the colored compound might be an oxonium salt. Now it is well known that certain  $\alpha\beta$  diketones and o-quinones yield red colored oxonium salts in acid solution (cf. Kehrman<sup>26</sup>). It appeared probable to us therefore that the red compound formed in the estrogen color reaction might be an oxonium salt of 3-hydroxy-16,17-diketoestratriene (XX), which, of course, under the conditions of the reaction would be partially sulphonated.



We saw that if this explanation was the correct one, the following would be expected to occur

(a) The red colored compound should be formed from estriol under much milder conditions than are necessary for its formation from estrone, since the  $\alpha\beta$  dihydroxy-grouping of the former should yield an  $\alpha\beta$  diketone more readily than would the  $-\text{CO}-\text{CH}_2-$  grouping of estrone.

This was found actually to be the case. Heating estriol with 50 per cent sulphuric acid, or with lead peroxide in acetone solution and subsequently acidifying, or with perchloric acid, all yielded the typical red color. These treatments did not result in the formation of a red color from estrone. In passing I might mention that Mr. Darrach has recently standardized the conditions for the color reaction of estriol with perchloric acid, so that it is now possible to determine quantitatively the amount of estriol in an estriol-estrone mixture by a direct process.

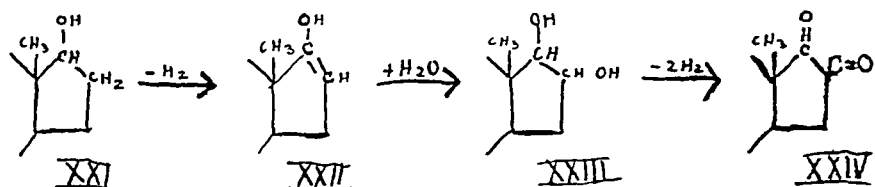
(b) The red color should be readily discharged by mild conditions of reduction, and the product should be partially sulphonated estriol and/or

a mixture of its  $C_{16}$  and  $C_{17}$  epimers, even though estrone was originally used in the reaction

We again found that our anticipations proved to be correct. From the mixture obtained by discharging the red color in an estrone color reaction with zinc, tin, or sodium bisulphite, a product was obtained which behaved like estriol, and unlike estrone, in that it gave a red color on heating with 50 per cent sulphuric acid.

We were finally convinced that our explanation of the mechanism of the color reaction was essentially correct, when we found that the red colored solutions deposited a solid insoluble product on treatment with o-phenylenediamine, since the formation of quinoxalines on treatment with this reagent is characteristic of  $\alpha\beta$ -diketones.

Shortly before we had arrived at this conclusion Pincus and Zahl<sup>27</sup> made the very important discovery that if estrone is administered to a pseudopregnant rabbit, or to an ovariectomized rabbit treated with progesterone, estriol appears in the urine. Experiments carried out on hysterectomized animals clearly showed that this *in vivo* hydration of estrone to estriol occurs in the uterus. Now, as has been seen, the main end-product of progesterone metabolism is pregnanediol, which is formed from the former by the addition of six hydrogen atoms. We therefore argued that if it was justifiable to assume from the work of Pincus and Zahl that the metabolism of endogenous estrogens in the pseudopregnant uterus is dependent upon the simultaneous conversion of progesterone to pregnanediol, then it might be logically expected to be a process involving the loss of six hydrogen atoms. That is to say we pictured endogenous estrogen being metabolized in the pseudopregnant uterus by a process involving three successive dehydrogenations in which progesterone was acting as a hydrogen acceptor. Now the work of Doisy and his co-



workers<sup>28</sup> points to estradiol as the true endogenous ovarian estrogen. We therefore speculated on what might happen to estradiol (XXI) as a result of a three-stage dehydrogenation. It seemed likely that it might first lose



two hydrogen atoms to yield the enolic form of estrone (XXII), which might then add on the elements of water to form estriol (XXIII). The latter by two successive dehydrogenations might be expected to yield 3-hydroxy-16,17-diketoestratriene (XXIV)—the chromogen which we believe is formed in the Kober color reaction.

These entirely speculative arguments therefore led us to anticipate that hydroxydiketoestratriene might prove to be one of the main end products of simultaneous estrogen and progesterone metabolism. We therefore undertook a search for this substance in human pregnancy urine. We have not so far isolated it, and since isolation in a state of chemical purity is the only entirely satisfactory proof of the existence of a compound, we cannot be sure that our theories are correct. We have, however, obtained strong indications that human pregnancy urine does contain a chromogen which is not estrone or estriol and which displays many similarities in behavior to the chromogen formed in the Kober color reaction. We are hopeful, therefore, that our speculations concerning estrogen metabolism may be not far from the truth.

This theory of estrogen metabolism permits a new light to be thrown upon two interesting papers that have recently been published. Smith and Smith<sup>29</sup> have shown that the yield of physiologically active estrogenic material obtainable from human pregnancy urine can be greatly increased by the addition of zinc to the urine during the acid hydrolysis. We consider that this phenomenon may be due to the reduction of the diketone to estriol or its epimers, rather than to the reduction of estrone to estradiol as the authors themselves suggest. Patterson<sup>30</sup> has recently described a method for the chemical diagnosis of pregnancy based on the colorimetric determination of estriol by the Kober reaction. His process involves a preliminary treatment of the urine with sodium bisulphite, which he believes facilitates the performance of the color reaction by destroying various pigmented substances in the urine. We believe that the observed improvement in the color reaction after sodium bisulphite treatment, may be due to the reduction of the diketone originally present in the urine to estriol and its epimers.

In conclusion I must apologize for devoting so much of my time to speculative theories. Speculation is a poor substitute for experimental work, but in a new and rapidly expanding field such as this, it is perhaps justified since it often provides the stimulus that leads to the making of new laboratory discoveries.

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## INFECTIOUS MONONUCLEOSIS\*

JOHN R. PAUL

IT is unnecessary to call attention to the fact that infectious mononucleosis is a disease which has been recognized for about fifty years under the term of glandular fever, but a disease which for the last fifteen years has been reclassified under a new name. Under the old name it was regarded more or less with indifference, under the new it has been rapidly accepted as a definite clinical entity, at least such has been the case in this country. Abroad, particularly in Germany, this has not been the case, and it is their loss, I should say. They still use in Germany the terms, "drusen-fieber" or "monozytenangina," both of which carry with them a non-specific implication which cannot be dispelled by even the most exhaustive of their studies.<sup>1 2</sup>

It is also unnecessary, as well as impossible, to give a full account of infectious mononucleosis in an article of this type. Such descriptions may be found in some of the well-known articles describing this disease.<sup>3,4 5</sup> Nor will I attempt to discuss the various theories of its nature, nor the experiments which have been done in a search for an etiological agent. Instead, this article will be limited in its scope essentially to the clinical diagnosis of this disease.

It is of course of first importance to gain an adequate impression of the clinical picture. Next, one should have some knowledge of the two most important laboratory aids, the blood picture and the serological test. A knowledge of all three features should then make the diagnosis easy. In fact I think I am correct in saying that there are few diseases in which we are so fortunate as to have three such definite diagnostic aids, and yet, in spite of them, the disease probably escapes recognition very often. One has to be distinctly on the lookout for it. Often the clinical symptomatology is very mild, there seems to be such a thing as "walking infectious mononucleosis" and these and other cases may easily escape recognition if differential blood counts do not happen to be done. In fact, it is easy

\* Delivered October 31, 1938 in the Eleventh Annual Graduate Fortnight

for a great blind spot for the disease to develop. Under some circumstances this blind spot is so great as to almost blot the disease out of existence. This may have been the situation which universally prevailed with regard to glandular fever during the period of the World War. Professor Tidy<sup>3</sup> of London states that between the years of 1915 and 1920 he could not find a single reference to it in medical literature. Today the Index Medicus lists about twenty-five papers a year under the title of infectious mononucleosis. But in spite of local interest in some places, the distribution of the disease continues to be irregular. A student of ours who recently spent a year in postgraduate medical work in London, where much good work has been done on this disease,<sup>3</sup> tells me that the professor of medicine in one of the best known of their medical schools, informed him that he had never seen a case of infectious mononucleosis. But we may be subject to these same blind spots here. How did the Mt. Sinai Hospital of New York City happen to collect such a large series in a short space of time unless they were on the alert for them? Why does the disease seem to be so particularly prevalent in medical students? Is it possible that it is recognized only in those cases of upper respiratory infection in which consecutive blood counts are frequently performed?

*Predisposing Features.* I have already stated that I am not going to try to cover the whole clinical picture of the disease. Instead, I am going to draw largely upon experiences gained from our series of cases. This series is small. It comprises only fifty-one cases which have been studied at the New Haven Hospital, although additional information has also been obtained from about forty more cases seen elsewhere. In some respects our series gives a different picture from that mentioned in the usual textbook article.

*Age.* Most of the cases in our series occurred in young adult males who were between the ages of twenty and thirty. Rarely has the disease been seen on our Pediatric Service. This experience is not universal (Chart 1). There have been epidemics in which the cases were confined largely to children,<sup>6</sup> or school boys.<sup>7</sup> A remarkable one, in which the diagnosis was confirmed by serological tests, is that reported by Nolan<sup>6</sup> from the U. S. Naval Station at Coronado, California, in which 220 cases are mentioned as occurring among the juvenile members of sailors' families. Only five of these cases occurred in adults.<sup>1</sup> The fact that it is a disease of young adults with us in New Haven, may be influenced by our university population, but I cannot believe that this is the sole deter-

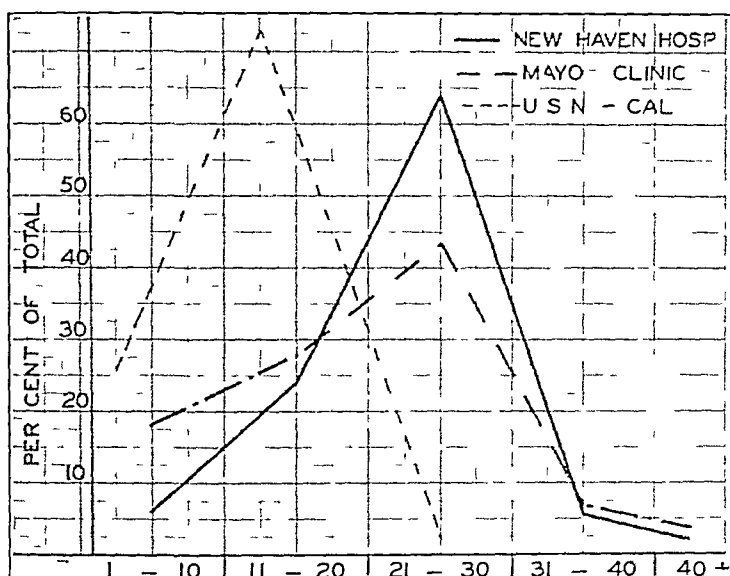


Chart 1—The age distribution of the New Haven Hospital series of 51 cases of infectious mononucleosis, compared with two other series *i.e.*, 44 cases reported by Heck of the Mayo Clinic,<sup>5</sup> and a series of 220 epidemic cases of Nolan from the U S Naval Station in Southern California.<sup>6</sup> This last series suggests that there may be a special juvenile form of the disease, perhaps more prone to occur in epidemics than the adult form

mining factor. Or, there may be a juvenile form of the disease which is prone to appear in epidemic form which we have not had the opportunity of seeing at our hospital.

**Occupation.** The use of the term infectious mononucleosis was first applied by Sprunt and Evans<sup>8</sup> to an acute illness of which six cases were described, four of which occurred in medical students. Since then there have been many comments on the extraordinary predilection which this disease has for students living in institutions, and particularly for medical students. Two-fifths of our cases occurred in individuals who were directly or indirectly associated with the New Haven Hospital (See Table 1).

But besides the "institutional" feature, whether medical or otherwise, the list of occupations in Table 1 indicates that we are dealing with a disease of those in sedentary employment. Is this because our patients happen to be individuals who are prone to be hospitalized for what

TABLE I

OCCUPATIONS OF 51 PATIENTS WITH INFECTIOUS MONONUCLEOSIS  
AT THE NEW HAVEN HOSPITAL

<i>Hospital "Attendants"</i>	<i>Others</i>
6 Medical students	8 Schoolboys or girls
5 Internes	8 University students
4 Nurses	3 Teachers
1 Technician	2 Bookkeepers
1 Social worker	2 Housewives
1 Orderly	2 Unspecified
1 Porter in hospital	2 Infants or children
1 Doctor's wife	1 Minister
	1 Architect
	1 Salesman
	1 Poolroom attendant
<hr/> 20	<hr/> 31

SEX                      Males 34 — Females 17

appears at first to be a trivial illness and they thus get the benefit of one or more blood counts? Certainly it is true that many cases are mild and the patient insists on remaining up and around, and probably this is more true than ever among the laboring class

## CLINICAL PICTURE

The clinical picture of infectious mononucleosis, as we know it, can be reviewed best here with the aid of a diagram illustrating clinical signs and laboratory tests exhibited by a more or less typical case (Chart 2) The diagram is helpful because the chronological order in which the signs appear is important To begin with, it is hardly enough to speak of infectious mononucleosis as a disease characterized by general glandular enlargement, by mononucleosis and by an increased titer for sheep cell agglutinins, unless we appreciate that none of these signs may be present during the first week of the disease

*Incipient Symptoms* In our series of cases the onset has often been insidious and marked by nonspecific features such as sore throat, malaise, pain in the shoulders and neck, leukopenia, and an irregular fever The temperature curve at this period is confusing It may be similar to that

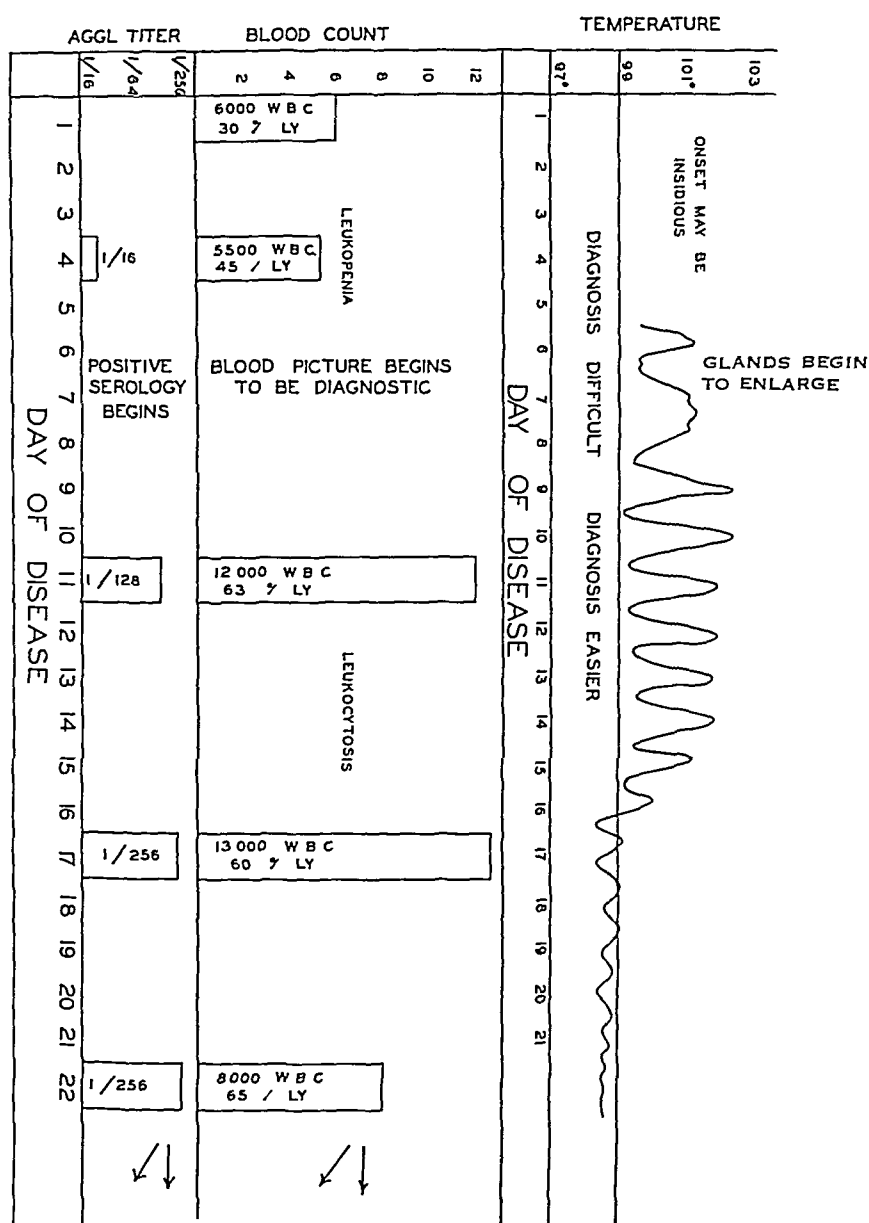


Chart 2—The course of a typical example of a moderately severe case of infectious mononucleosis, illustrated by the temperature curve, the blood picture, and the serological reactions



TABLE II

SYMPTOMS AND SIGNS DURING THREE STAGES OF THE DISEASE AND THE PERCENTAGES IN WHICH THEY ARE RECORDED IN OUR SERIES

<i>Prodromata or Early Symptoms</i> <i>(Exclusive of fever and headache which is very common)</i>		<i>Important Signs and Symptoms of the 1st and 2nd Week of the Disease</i>		<i>Late and Convalescent Symptoms</i>
Sore throat	46%	Swollen glands	60%+	Glands may remain large for weeks
Malaise	38%	Red throat	} 60%	
Swollen glands	15%	Patches on tonsil		
Chills	15%	Stomatitis		
Cough	15%	Petechiae on soft palate	10%	Severe cases may leave patients feeling below par for months
Eyes sore or pain behind eyes	12%	Exchids swollen	10%	
Neck sore or stiff	12%	Jaundice	10%	
Pain in shoulder	6%	Rash	10%	
Pain in abdomen	6%			

seen in a mild case of typhoid fever. Chilly sensations are frequent at the onset and the fever is often up in the evening to  $101^{\circ}$  or  $103^{\circ}$  and down the following morning, so that for the first few days of the illness the patient may get up and go to his work as usual. This fact often confuses the physician, who, like the patient, may require several days to make up his mind that he is dealing with someone who is really sick. Thus, it is often not until the end of the first week that the diagnosis is established.

By the end of the first week the glands may be sufficiently enlarged to attract attention and the blood count also begins to become diagnostic. At about this time the sheep cell agglutinins may have risen to a titer of  $1/32$  or above, which is also diagnostic.

*Signs and Symptoms of the Full-blown Disease* The classical physical signs of the disease are too well known to require attention here. That is, an acute illness of ten days to three weeks duration in which there is a gradual enlargement of lymph glands which does not go on to suppuration, enlargement of the spleen, a red throat and stomatitis often accompanied by patches on the tonsils and pharynx and with lesions with which Vincent's organisms are associated. The frequency with which some of these were found in our series is listed in Table II. Here the percentages with which these occurred are probably relative, because all of the items were not searched for diligently in every case. Three clinical

features which are not common but striking when they occur, will be mentioned briefly

(a) *Ocular symptoms* probably occur more frequently than one would be led to believe. In their early stages they are characterized by pain in the eyes, or pain back of the eyes which regresses during the second week but leaves the patient with puffy eyelids. This may be a striking finding.

(b) A *papulo-macular rash* is an irregular symptom but one which has been emphasized, and properly so, by Tidy.<sup>3</sup> The eruption is diffuse or patchy and generally limited to the trunk. It is difficult to describe other than by the term morbilliform, in two of our cases it was classified by the attending physician as a "drug rash." It may be preceded, or accompanied by an enanthem consisting of petechiae on the soft palate.

(c) *Jaundice* is another manifestation present in the second or third week of the disease. It is often definite and striking. A recent report from Sweden emphasizes its importance.<sup>9</sup>

*Convalescence* Infectious mononucleosis is a benign condition which is self-limiting in two or three weeks. However, it may be a long time (perhaps six months) before the glands return to normal size, and a long time before the patient feels like himself again. So prominent is this post-febrile depression that in severe cases it seems to be part of the disease. One of our patients ran a low grade fever for six weeks and was more or less prostrated during this whole period.

*Blood Picture* Half of our cases showed an appreciable leukopenia during the first week of the disease. Here the counts ranged about 4,500 per c mm., the lowest being 2,000 which occurred in two cases. This results from a granulocytopenia and during the first and second weeks one finds, besides this sharp reduction of polymorphonuclear neutrophils, a decrease in filamentous forms giving rise to a so-called toxic blood picture. The disease may start, therefore, with an acute granulocytopenia and it may be worth considering what relationship this bears to the oral lesions, which, it will be recalled, are common in agranulocytosis of other types. During the first week the lymphoid cells may range from 28 to 60 per cent. It is also my impression (although I have not had occasion to confirm the degree to which this is true) that the characteristic abnormal lymphoid cells, so common in this disease, generally do not appear in diagnostic numbers at this time. In other words, one is fortunate if one can make a diagnosis from the blood picture during

the first week

By the second week the total white count increases to give rise to a leukocytosis which may range from 8,000 to 20,000 leukocytes per c mm. At this time lymphoid cells are found in from 40 to 85 per cent. This then is the stage of lympho-mononucleosis in which large and characteristic cells appear in considerable numbers in the blood. It is well known that some observers consider these cells to be absolutely diagnostic of the disease, others do not. Downey and McKinlay<sup>10</sup> gave in 1923 one of the best of the early descriptions of these lymphoid cells in infectious mononucleosis (or what they called acute lymphadenosis). In their article there is a colored plate drawn fifteen years ago but adequate for our purposes today. Here they describe three types of lymphoid cells distinguishable from the cells of acute lymphatic leukemia. Their differential point was, and still is, that the predominating large lymphoid cells of infectious mononucleosis are mature cells, in contrast to the immature cells of acute lymphatic leukemia.

Osgood<sup>11</sup> has later demonstrated that immature cells (lymphoblasts) may be found in infectious mononucleosis but that a more mature cell, for which he uses the term *prolymphocyte*, is the more typical cell. In size these are larger than polymorphonuclear leukocytes and this alone is enough to differentiate them from normal lymphocytes. Furthermore, the nucleus may have prominent nucleoli or intranuclear bodies and also fenestrations within the cell. Osgood believes these fenestrations to be another diagnostic sign in infectious mononucleosis.<sup>12</sup>

The characteristic blood picture with a leukocytosis ranging from 8,000 to 20,000 cells and the relative lymphocytosis with representatives of the lymphoid series above described, is probably a late (second and third week) manifestation of the disease. By the end of the third week the total leukocyte count drops, as do also the percentages of lymphoid cells. Leukopenia during convalescence lasting for some weeks or months, has been described.<sup>3</sup>

The red count is unaltered throughout the course of the disease, and this is another point helpful in eliminating lymphatic leukemia where anemia is so common.

#### SEROLOGIC DIAGNOSIS

Reference has already been made to the presence of a unique and easily demonstrable antibody in this disease. Its discovery was the result

of an accidental finding and its real significance is still unexplained. Like the Wassermann test it is essentially a nonspecific reaction, but in syphilis we know the etiological agent, whereas in this disease we do not.

The story of this finding takes us back to the work of Forssman,<sup>13</sup> who in 1911 recognized the existence of certain principles with regard to the nonspecificity of certain antigen-antibody reactions. He demonstrated serological relationships between substances (now recognized as non-protein "haptens") in the cells of animals widely separated in the zoological system. The antibody in these reactions was, and has been described, therefore, as the Forssman antibody, but to define a Forssman antibody is difficult. Perhaps, as suggested by Landsteiner,<sup>14</sup> now that we know more about such antibodies and particularly their variations, the term "heterogenetic" or "heterophile" should be more properly applied to reactions of antibodies with antigens which are not related in their origin.

Only recently has the application of the Forssman principle found its way into clinical medicine. This occurred when Davidsohn<sup>15</sup> studied the "heterophile" response, in the form of lysins and agglutinins for sheep cells (erythrocytes), in the serum of patients who had been injected with horse serum. Horse serum contains a heterophile antigen and so it was natural that when it was injected into man, there should be a heterophile antibody response. Soon afterwards, during the course of a search for heterophile antibody responses in various clinical conditions, a high titer of such antibodies was discovered in the blood of patients with infectious mononucleosis.<sup>16</sup> Later Bunnell<sup>17</sup> proved that this finding was sufficiently unique to be of diagnostic value in this disease. The use of the test has increased the degree of confidence with which the disease can be diagnosed. Whether this is responsible for increasing the number of cases in our series is not known, but in any event from 1923 to 1930 we had only twelve cases, whereas in a similar length of time, from 1930 to 1936, we have had thirty cases.

It should be pointed out that normally, sheep cell agglutinins exist in low titer in the sera of most individuals. Seldom is this titer above  $\frac{1}{8}$ . In horse serum disease this titer may be enhanced up to  $\frac{1}{64}$  or higher. The normal antibody, which is easily demonstrable in the form of sheep cell agglutinins, and the serum disease antibody adhere to the type originally described by Forssman and originally known as the "Forssman antibody." In infectious mononucleosis the heterophile antibody exhibits

certain differences<sup>18</sup> which are sufficiently clear cut to differentiate it from this original "Forssman antibody." This difference can be readily brought out by absorption tests,<sup>19,20</sup> and these tests are not too complicated for the average clinical laboratory. At first thought it would hardly seem as if such a differential test would have much clinical value, for not often would serum disease and infectious mononucleosis be confused. But, as a matter of fact, it does have a clinical value and an important one. This is particularly true in the case of patients suspected of having infectious mononucleosis but in whom the titer is low ( $1/16$  or  $1/32$ ). Here it is necessary to know whether one is dealing with what I shall refer to as the "I M" antibody, or whether one is dealing with the antibody which occasionally exists in normal individuals. As early diagnosis is to be desired in this, as well as in other diseases, and as the titer of agglutinins is apt to be low ( $1/16$  or  $1/32$ ) in the early stages of this disease, the clinical value of the differential (absorption) sheep cell test immediately becomes apparent.

*Appearance Time and Duration of Agglutinins* The general course of the serologic reactions in infectious mononucleosis is shown schematically in Chart 2. In the first week the titer is usually low ( $1/16$ ). In the second and third weeks it averages  $1/256$  or slightly higher. Titers as high as  $1/2000$  were encountered twice in our series during this period of the disease.

Much work remains to be done with regard to the duration of the elevated sheep cell agglutinin titer. By and large, it is safe to say that it disappears fairly quickly, or, in other words, this antibody is apparently more transient than that seen in virus diseases or in a bacterial disease such as typhoid fever. Often the level had dropped to  $1/8$  by the fifth or sixth week in our series of cases of infectious mononucleosis. In one case, to which I have already referred, it remained at a level of  $1/64$  for seven weeks and the patient continued to have fever, mononucleosis and considerable malaise during this period. This patient eventually recovered but we believe that she represented an example of a chronic or subacute form of the disease. Exceptionally high titers may also require many weeks before returning towards normal, as in the case shown in Table III.

\* Actual details of performing these serological tests will not be given in this article. For methods there are many sources to which the reader may be referred.<sup>9</sup> It should be mentioned however, that one of the main features of the test for the differentiation of the I M antibody from the normal sheep cell agglutinin is that the I M antibody is but slightly or partially absorbed by suspensions of guinea pig kidney, whereas the normally occurring sheep cell agglutinin is wholly absorbed by this antigen. For a description of the methods of performing these tests the reader is referred to the work of Beer<sup>19</sup> and of Davidsohn.<sup>20</sup>

TABLE III

BLOOD COUNTS, SHEEP CELL AGGLUTINATIONS, KAHN AND WASSERMANN REACTIONS IN A CASE OF INFECTIOUS MONONUCLEOSIS

Date	Day of Disease	W B C	Lympho- cyte %	Sheep Cell Agglutinin Titer	Kahn	Wassermann Alc	Chol
1/10/38	13	6,050	49	1 512	++++	—	++++
1/15/38	18	4,500	21	1 4096	++++	—	++++
1/22/38	25			1 2048			
2/ 5/38	39			1 512	++		++++
2/11/38	45	7,050	28	1 512	+	—	—
2/19/38	53			1 512	+	—	++
3/ 5/38	70			1 256	—	—	—
4/ 5/38	101			1 256	—	—	—

A recent report from Japan<sup>21</sup> describes the results with convalescent sera which were tested from about ten patients. Blood was obtained from one to three months after the acute illness. Half of them still showed a titer of 1/16 or over. Two were still above 1/64.

*Cases with Negative Serology* Another question is, how frequently does this reaction fail to occur in proven cases of infectious mononucleosis. In the New Haven series, one or more tests were performed upon thirty-seven patients and in only four of these did the titer prove to be less than 1/32. In other words, 90 per cent of our cases had positive serology. This may indicate that we are relying too much upon the sheep cell test for our diagnosis. In Nolan's<sup>6</sup> epidemic series, previously referred to, he mentions that all of those tested among his total of 220 cases had agglutinins of from 1/20 to 1/320.

On the other hand, Davidsohn<sup>22</sup> who has done extensive work on this subject has stated that it may be necessary to designate many patients by the term, *seronegative* cases of infectious mononucleosis. From the Mt. Sinai Hospital<sup>23</sup> comes the surprising statement that the heterophile antibody reaction is positive in only 40 per cent of the cases. Obviously, much more work is needed on this point, particularly as there is as yet little data as to what the differential (absorption) test would reveal in the cases with low titers and presumably negative tests.

*Positive Wassermann or Kahn Reactions* Shortly before the heterophile test began to be used in this disease, a report from Germany described a temporarily positive Wassermann reaction in a patient suffering with what was called *Monozytenangina*.<sup>24</sup> This was in 1928. In 1930

Weber,<sup>25</sup> in England, called attention to the fact that in glandular fever temporarily positive serological tests for syphilis may occur. Several reports have subsequently followed, among the most recent is that of Bernstein<sup>26</sup> from the Johns Hopkins Hospital. In his series of thirty-seven cases a false-positive Wassermann reaction was noted in six.

Thirty-eight cases from the New Haven Hospital series have had serological tests for syphilis and of these, three yielded positive results either by the Kahn or Wassermann test. This is not a high percentage—that is, 8 per cent. It may be compared with the 16 per cent incidence of positives noted in the Johns Hopkins series. In both series, however, the routine tests for syphilis were probably made early in the disease. Had they been made upon samples of blood taken late in the disease, it is quite probable that the incidence of transiently positive reactions would have been higher. In fact, this is suggested by the Japanese observation,<sup>21</sup> noted earlier in this paper, in which samples of sera were obtained and tested from one to three months after the acute disease. About 40 per cent of these sera are listed as having a positive Wassermann!

When this does occur it is indeed striking, as is to be seen in one of our cases, reported by Sadusk<sup>27</sup> (See Table III). Here the Kahn, Wassermann and heterophile antibody tests returned towards normal more or less simultaneously. This again raises questions about the significance of the peculiar antibody or antibodies present in this disease. Surely no ordinary bacterium with which we are familiar, can cause such an immune response. Consequently, although the problem of etiology may be said to be still open in this disease it would at least seem, from immunological evidence, that an ordinary bacterium can perhaps be eliminated.

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ternal Diseases of the Eye" and "Operative Ophthalmology." He and Doctor Holloway wrote on "Pulsating Exophthalmos," and edited with Doctor Jackson "The Ophthalmic Year Book" for a number of years.

One of Doctor de Schweinitz's most dominant characteristics was his willingness to assist younger men in their work. He was never too busy to advise young ophthalmologists, who affectionately called him "King George" because of his distinguished appearance and bearing. His generosity to younger men was shown by his eagerness to collaborate with them in writing articles. He enjoyed writing, and loved to help his assistants obtain recognition for their literary contributions. He had an exceptionally alert mind and had such a concise, clear view of so many things that it could not but be reflected in the writings of the younger men he taught. He was deeply interested in scientific research and gave encouragement, assistance and unstinted praise to those who achieved results. He had hosts of friends, both in and out of the medical profession and many benefited by his skill as surgeon and ophthalmologist.

In writing the history of ophthalmology in the twentieth century, the work of George Edmund de Schweinitz will stand out with that of other great men like Wilmer and Fuchs. It is certain that the inspiration from his work and character will continue to be a force driving ophthalmology to ever greater heights.

CONRAD BERENS

#### DEATHS OF FELLOWS

DENENHOLZ, AARON 1904 Avenue I, Brooklyn, New York, born in Austria, June 16, 1875, died in Brooklyn, New York, December 1, 1938, graduated in medicine from the New York University Medical School in 1897, elected a Fellow of the Academy, December 3, 1908.

Dr Denenholz had been at one time consulting gynecologist to the Manhattan State Hospital.

FORD, WILLIAM MILLER 130 East 67 Street, New York City, born in Brooklyn, New York, November 30, 1878, died in New York City, November 26, 1938, graduated in medicine from the University of Virginia in 1899, elected a Fellow of the Academy Mar 3, 1904.

Dr Ford, who was a former president of the medical board of St. Vincent's Hospital, was attending surgeon to that institution from 1905-26 and director of gynecology from 1927-31. He was consulting gynecologist to the New York Hospital for Ruptured and Crippled since 1921 and clinical professor of obstetrics at New York University from 1920-33.

Dr Ford was a Fellow of the American College of Surgeons, the American Medical Association and a member of the New York Obstetrical Society and the County and State Medical Societies.

LALLY, JORDAN 30-60 29 Street, Long Island City, New York, born in Philadelphia, Pennsylvania, December 2, 1893, died in New York City, November 26, 1938, graduated in medicine from the University of Vermont in 1921, elected a Resident Fellow of the Academy April 2, 1931.

Dr Lally was a member of the American Medical Association, the American Public Health Association and the County and State Medical Societies.

SITTENFIELD, MAURICE JOSEPH 29 West 74 Street, New York City, born in Lubarsch, Germany, March 17, 1877, died in New York City December 1, 1938, graduated in medicine from Bellevue Hospital Medical College in 1898, elected a Fellow of the Academy November 7, 1912.

Dr Sittenfield was at one time associate surgeon to the Mount Sinai Hospital. From 1909-34 he was assistant professor of pathology at the College of Physicians and Surgeons.

Dr Sittenfield was a Fellow of the American Medical Association, a Fellow of the American College of Radiological and a member of the Radiology Society of North America, the American Radium Society, the American Association of Pathologists and Bacteriologists, the American Association for Cancer Research, the New York Pathological Society and the County and State Medical Societies.

Dr Sittenfield was the author of many papers and articles on radiology.

BULLETIN OF THE NEW YORK  
ACADEMY OF MEDICINE

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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



FEBRUARY 1939

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THE SIGNIFICANCE OF THE ALBUMIN  
FRACTION OF SERUM

*Harvey Lecture, November 17, 1938*

A ASHLEY WEECH

SERUM ALBUMIN is to be defined as that fraction of the protein of serum which remains in solution after half saturation with ammonium sulphate or which is not salted out in a 21.5 per cent solution of sodium sulphate. The fractions which are removed by these procedures are globulins. Serum albumin, so defined, possesses physiologic characteristics which are distinct from those of the globulins. It is important in maintaining the volume of the blood and it is essential to the flow of fluid across the capillary wall. These properties are intimately concerned with the general phenomenon of the circulation of the blood, a circumstance which makes it peculiarly appropriate that they be discussed before the Harvey Society. Moreover, the physiologic properties of serum albumin are of great importance in medicine for the amount of albumin which circulates in the plasma is easily depleted when health is disordered. An understanding of this process of depletion, and its converse, replenishment, is essential to correct appraisal of the significance of the albumin fraction of serum.

In selecting material in a large field from which to prepare this eve-

ning's lecture, I have perforce given preference to investigations which have occupied the attention of workers in the laboratory which I represent. A few aspects only can be included of the important role of serum albumin in regulating the distribution of fluid between capillaries and tissue spaces, this phase of the subject has been covered in a recent Harvey Lecture by Eugene M. Landis.<sup>1</sup> Likewise, Cecil K. Drinker<sup>2</sup> has brought before you some of the problems which require elucidation in connection with the occurrence of serum proteins in lymph and I shall not enter this field of controversy. Since familiarity with ground to be covered will aid in orientation, I shall begin by presenting an outline.

Part I Effect of diet on serum albumin concentration

- a The process of depletion
- b The process of replenishment

Part II Physiologic importance of serum albumin

- a Fluid distribution and edema
- b Absolute and relative permeability of capillaries
- c Regulation of blood volume

Part III Medical control of serum albumin deficiency

- a Injection of acacia, transfusions with serum and blood
- b Diet, qualitative differences among food proteins in promoting albumin synthesis

## PART I

In 1929 Frisch, Mendel, and Peters<sup>3</sup> reported that young rats fed on diets composed chiefly of carrots developed deficits in serum protein. The diet was deficient in protein, but otherwise adequate. In 1931 Shelburne and Egloff<sup>4</sup> described the development of hypoproteinemia in a dog during maintenance on a low protein diet. These observations have been used in the laboratory of the Babies Hospital to provide a method<sup>5, 6</sup> for depleting the serum albumin. Our story can be opened by observing the method.

Dogs are maintained on a low protein diet, the composition of which is indicated in Table I. The quantities listed are the amounts given to each dog per day. Animals subsisting on the diet have always exhibited a negative balance of nitrogen. Metabolism observations indicate an average daily loss of nitrogen of 1.15 gm. The biological effects of subsistence on the diet appear to be referable to deficiency of protein alone. When the diet is supplemented with casein it has proved adequate for maintenance.

of health The addition of extra amounts of various vitamins<sup>7</sup> has not altered the course of experiments

TABLE I  
COMPOSITION OF LOW PROTEIN DIET

	grams
Carrots	300
Rice	35
Lard	40
Cod liver oil	10
Sugar	115
Salt mixture	5
Water, sufficient to make	900

Furnishes 1200 calories, 1.23 gm nitrogen

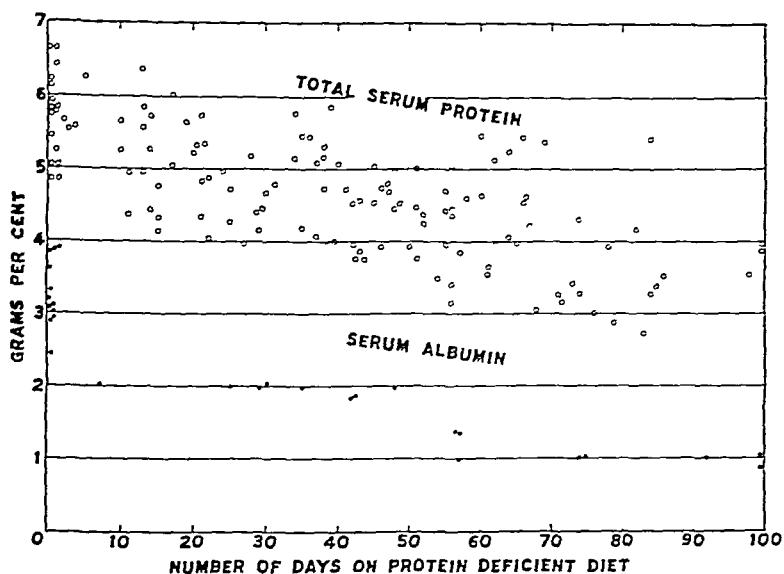


Chart 1—Concentration of albumin and total protein in the serum during maintenance on the low protein diet. From the *Journal of Experimental Medicine* <sup>6</sup>

7

Chart 1 shows the results of 150 determinations of the albumin and total protein of serum in twenty-one dogs during maintenance on the diet. The downward trend of albumin and total protein with continuance of the diet is pictured clearly. In Chart 2 the trends are shown by average lines and the course of the globulin fraction is depicted. The average concentration of globulin remains singularly constant, it follows that the fall in total protein is brought about entirely by depletion of the albumin fraction.



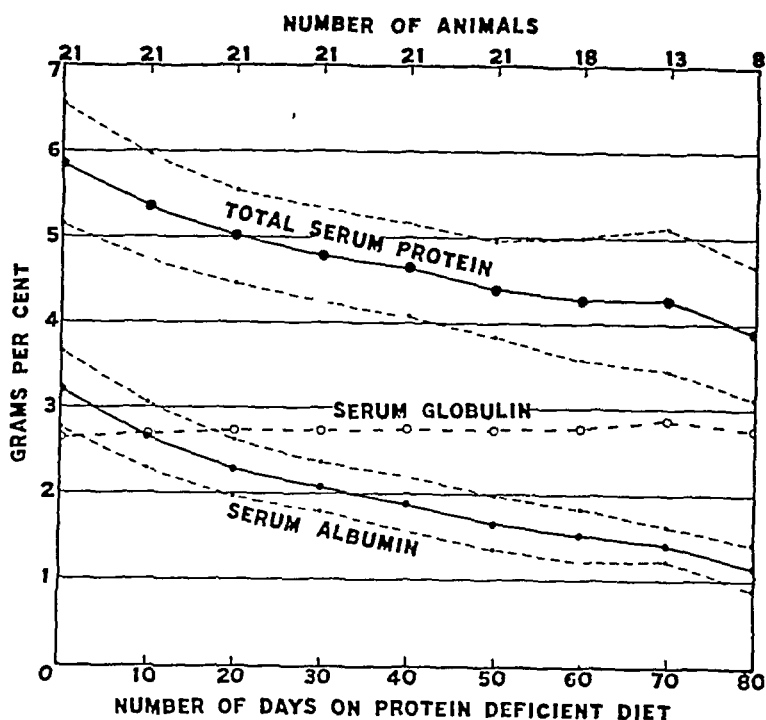


Chart 2—The average trends of albumin, globulin, and total protein during maintenance on the low protein diet. The dotted lines above and below the unbroken lines for albumin and total protein are placed at a distance of one standard deviation from the average values. From the *Journal of Experimental Medicine* <sup>6</sup>

There are two additional points concerning the depletion of albumin. The first can be seen from the chart, namely, that the rate of decline is more rapid during the initial days or few weeks of maintenance on the diet than subsequently. On the average it requires eleven weeks to double the fall in concentration which develops in three weeks. The slowing in the rate of decline with the passage of time has been shown in metabolism studies to be associated with a progressive diminution in the nitrogen lost by the body. There is thus portrayed an adaptive ability of the body in adjusting its metabolic processes so as to spare protein. A similar adaptive ability has been described in humans<sup>8</sup> during subsistence on low protein diets and the process has been shown to be associated with a fall in the basal output of energy<sup>9, 10</sup>

A second and curious fact concerning the depletion of albumin is that

the rate of fall is independent or almost independent of the amount of energy consumed in the diet. One might well have expected that a high intake of calories in the form of carbohydrate and fat would not only protect the body nitrogen but also slow to a minimum the depletion of protein in the serum. This does not appear to be the case. We have not been able to discern that the decline is more rapid during fasting than when the energy intake is liberal. Among eighty-three animals in which the daily dietary calories varied from fifty to eighty-seven per kilo of weight, the coefficient of correlation between energy intake and percentage albumin depletion after three weeks was only 0.11, a degree of association entirely devoid of statistical significance.

We have now seen that the simple procedure of maintaining a dog on a low protein diet not only allows the production of serum albumin deficits in a laboratory animal and thereby affords the means for observation of the consequences but also that some features which characterize the process of depletion can be made out. It will be instructive to watch the process in reverse so as to learn something of the nature of regeneration.

In the first group of experiments<sup>11</sup> moderate albumin depletion was obtained by administering the low protein diet to four dogs for a period of three weeks, the diet was then supplemented by the addition of beef so that each animal would receive eighty calories and 5 gm. protein per kilo. The degree of albumin depletion can be seen in Table II by comparing the initial levels in the first column with the levels in the second column which represent analyses at the end of the depletion period. Subsequent daily levels when the diet was supplemented with beef are shown in the remaining columns. The result was the same in each of the four experiments, it can be visualized best by a graph, Chart 3, showing the average course of regeneration. The course can be described with close approximation by a straight line. In two of the four experiments the regeneration was followed until the albumin had attained its previous level of health. Within the limits of experimental error there was no break in the straight line path of albumin concentration until this level was reached. Thereafter, no further regeneration occurred. These experiments are informative because they dispose of an idea which has been expressed or implied in recent literature, namely, that the strength of the stimulus for regeneration of albumin is proportional to the degree of albumin depletion. Apparently the stimulus is constant so long as any de-

TABLE II

*Days on Regeneration Diet*

<i>Dog</i>	<i>Before Depletion</i>	<i>0</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>
7-31	3 65	2 82	3 17	2 97	2 99	3 28	3 28	3 65	3 52	3 64	3 63		3 61	3 64
5-31	4 22	3 08	3 04	3 13	3 42	3 50	3 68	3 93	4 10	4 12	4 18	4 11	4 30	4 24
8-04	3 57	2 56	2 58	2 71	2 79	2 81	2 83	2 94	2 88	3 12	3 18	3 14		3 26
9-51	3 98	2 96	3 06	3 09	3 26	3 32	3 31	3 58	3 53	3 60	3 75			
Average	3 86	2 86	2 96	2 98	3 12	3 23	3 28	3 53	3 51	3 62	3 69			

Results of daily determinations of serum albumin concentration during regeneration on 1 diet which furnished 5 grams of protein per kilo. The added protein was in the form of beef muscle (chuck). The figures refer to grams per 100 cc serum. From the *Bulletin of the Johns Hopkins Hospital* 11

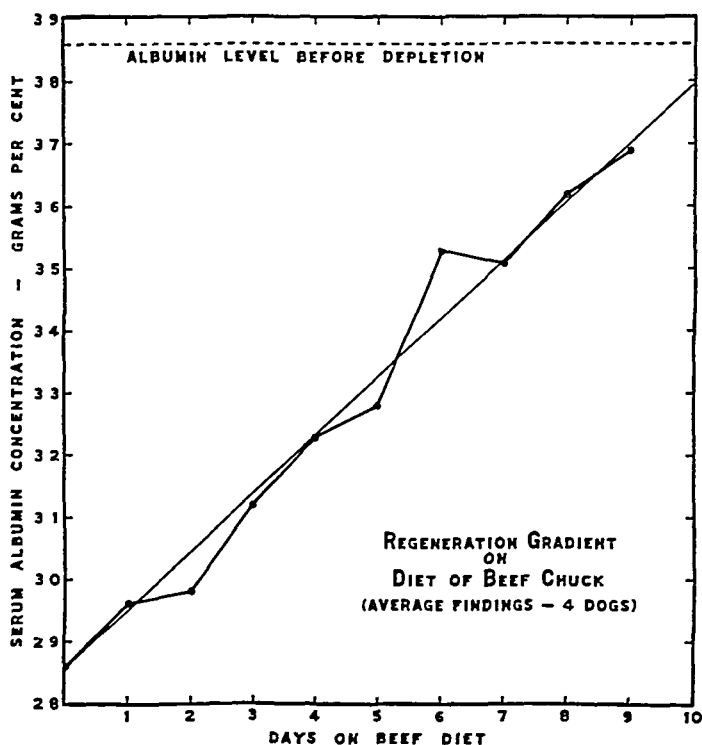


Chart 3—From the *Bulletin of the Johns Hopkins Hospital* <sup>11</sup>

pletion exists. When the intake of food is constant, a fixed amount of the diet will be utilized each day for fabrication of albumin. The experiments are further informative because the result can be contrasted with the type of regeneration which occurs under other conditions, conditions in which we incline to the opinion that the body mechanism responsible for synthesizing albumin has been impaired. From this point of view the straight line regeneration curve can be regarded as exemplary of the type of regeneration to be expected when the mechanism for forming albumin is normal.

Within recent years the accumulation of clinical evidence has shown that chronic depletion of the serum albumin is apt to be associated with disease of the liver. In 1932 Thompson, Ziegler, and McQuarrie<sup>12</sup> reported a case of hypo-albuminemia and chronic edema in a girl, aged two and one-half years, who failed to exhibit a rise in serum albumin or alleviation from edema when given a diet upon which the nitrogen balance was positive. Since there was no loss of albumin in the urine to explain

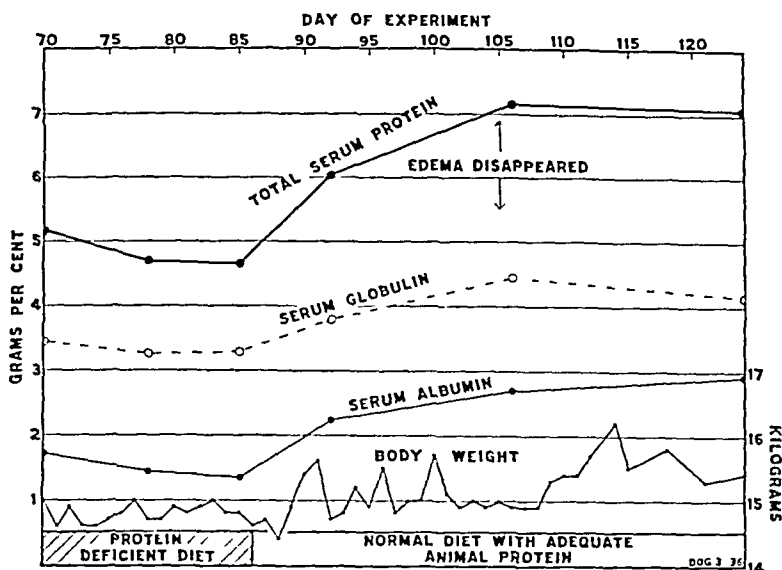


Chart 4—The regeneration of serum albumin in a dog debilitated by prolonged subsistence on the low protein diet. Before depletion the albumin concentration was 3.9 gm per cent. The lowest level was 1.4 gm per cent on the eighty-fifth day. After thirty-eight days of adequate feeding it had risen to 2.9 gm per cent. From the *Journal of Experimental Medicine* 6

the serum deficit, the authors suspected a defect in the body in the process of manufacturing serum protein. In a later communication,<sup>13</sup> 1936, after the patient had come to autopsy, it was reported that she had suffered from primary atrophy of the liver. In 1933 a similar case was described by Myers and Taylor,<sup>14</sup> in this patient liver injury was suggested by the results of tests of liver function. In 1935 Myers and Keefer<sup>15</sup> discussed the relationship between depleted serum protein and cirrhosis of the liver, they explained the low serum protein as being the result of alteration in the function of the liver. The writer<sup>16</sup> has cited the case of an infant in whom low serum albumin and edema were apparently caused by syphilis which involved the liver extensively. Such circumstances make it relevant to inquire concerning the status of this function of the liver in other types of hypo-albuminemia, namely, in the types found in nephrosis and in chronic malnutrition.

That the mechanism for forming albumin may be impaired by prolonged malnutrition is suggested by several of our experiments with

dogs<sup>6, 11</sup> When the time of maintenance on the low protein diet is lengthened to cover a period of several months, health and vitality are affected markedly, and replenishment of the albumin deficit is sometimes a protracted and difficult process This state of affairs is illustrated by the experiment outlined in Chart 4 With this animal after eighty-five days on the low protein diet the albumin had fallen from 3.9 to 1.4 gm per cent, the appetite had failed, vitality was low, and it seemed that life could not continue for more than a few days From this time on an adequate and varied diet was offered daily, because of anorexia small amounts only were eaten at first and life was sustained by gavages of milk A detailed record was not kept of the amount of food consumed daily but it is clear that the intake of both protein and energy increased slowly as strength and health returned The behavior of the serum albumin concerns us here During the first week the rise in concentration was rapid from 1.4 to 2.3 gm per cent, during the next two weeks the rise to 2.7 gm per cent was much slower, after three more weeks a level of only 2.9 gm per cent had been attained Thereafter, the gains continued but were extremely slow After six months a level of 4.0 gm per cent had been reached which was slightly above the previous concentration of health With this animal, after an initial rapid response to food, subsequent albumin regeneration was slow and apparently independent of the quantity of food consumed The form of the regeneration curve is impressively different from the straight line found in animals after short periods of depletion when health and vitality are not obviously impaired The slow approach to normal suggests that replenishment is being delayed pending restoration to normal of the organ concerned in the synthesis of albumin

If one accepts for the moment the possibility that liver injury was responsible for the delayed replenishment of albumin in this experiment, it is important to note that the injury was one which did not affect the early rate of synthesis but rather that it fixed at a subnormal value the level which could be reached This observation may have considerable clinical significance The constant low levels of albumin in patients with cirrhosis of the liver are similar, in such cases the initial response to an improvement in the diet is often meager, and complete recovery does not take place because the liver damage is permanent In many cases of nutritional edema in humans, there is found upon institution of adequate feeding the same initially rapid and subsequently slow regeneration of

albumin as in our experiments with dogs. Such regeneration curves suggest that the synthesis of albumin may be impaired in man as in the dog by prolonged malnutrition. In the form of Bright's disease called "nephrosis," it has been customary to regard the extremely low levels of albumin in the serum as due entirely to loss of albumin in the urine. That defective synthesis of albumin may also play a part in maintaining the depletion is suggested by the constant nature of the albumin level in the serum in some patients over long periods when protein intake and degree of albuminuria are varying widely. In one of the cases reported by Keutmann and Bassett,<sup>17</sup> observations are recorded over a period of seven months during which the patient always received an adequate caloric intake. However, the diet was changed from time to time to include a number of food proteins at levels which varied from 68 to 180 grams per day. To a certain extent increases in dietary protein were associated with greater loss of protein in the urine, nevertheless, the higher intakes also produced significantly greater storage of nitrogen in the body. Under the circumstances it is noteworthy that during the entire seven months the concentration of protein in the serum remained almost constant at a level near 3.9 gm per cent. Such constancy of serum protein concentration is difficult to understand in terms of defective kidney function alone. However, it is not difficult to explain if one admits the possibility of defective albumin synthesis of a type similar to that observed in our experiments with dogs.

In summary of Part I of this presentation. The administration of a low protein diet to a dog results in a progressive decrease in the concentration of albumin in the serum, the decline is at first rapid, later more gradual. A return to adequate feeding is followed by regeneration of the albumin. When the period of depletion has been short and the vitality of the animal is not impaired, the regeneration is rapid and on a constant diet follows a path of equal daily increments until the concentration of health has been regained. After long and debilitating periods of depletion, the regeneration, although initially rapid, is subsequently retarded and approaches the concentration of health very slowly. It has been suggested that the delayed type of regeneration may result from injury of the mechanism concerned in synthesizing albumin, a mechanism presumably located in the liver. Finally, data have been presented which intimate the existence of similar phenomena in several types of disease in humans.

## PART II

Your attention must now be turned to the importance in physiology of the albumin fraction of serum. I have already stated that it is not necessary to discuss fully the role of albumin in the control of fluid distribution at the capillary boundary since a number of aspects of this subject were covered in a previous Harvey Lecture. We may, however, record with pride that a New York physician, Epstein,<sup>18</sup> was the first to suggest that hypoproteinemia is the direct cause of edema in nephrosis and, we should fail to give honor where honor is due if we did not mention the great physiologist, Starling,<sup>19</sup> who first perceived the importance of the osmotic pressure of the protein of serum in preventing the passage of the fluids of plasma across the wall of the capillary into the tissues. It is interesting, however, that general acceptance of the postulates of Starling did not occur until Leiter,<sup>20</sup> 1928, and Barker and Kirk,<sup>21</sup> 1930, demonstrated that edema could be produced in otherwise healthy dogs by plasmapheresis, a mechanical method for removing plasma protein rapidly from the circulation.

That a correlation exists between the level of serum albumin and certain types of edema is now firmly established. With nephritic patients Moore and Van Slyke<sup>22</sup> found that an albumin concentration below  $2.5 \pm 0.2$  gm per cent was usually associated with edema. In malnutrition Bruckman and Peters<sup>23</sup> reported that edema almost always develops when the albumin falls below 3 per cent. In a study of nutritional edema in China,<sup>24</sup> dropsy was not observed when the albumin was greater than 3.0 per cent and was generally present when the level was less than 2.5 per cent. The relationship between albumin and edema in the experimental edema of dogs<sup>25</sup> is shown in Chart 5. The black dots represent analyses of plasma made when edema was present and the open circles refer to estimations before edema had developed or in a few instances after it had disappeared. Edema rarely appeared before the albumin was below 2 per cent, it was more often present than absent when the albumin was between 1 and 2 per cent, below 1 per cent edema was always present. Between globulin and edema no correlation can be discerned and the slight correlation in the total protein column obviously results from the albumin component.

The effectiveness of serum albumin in preventing edema depends upon its osmotic pressure. This pressure is exerted across the wall of the



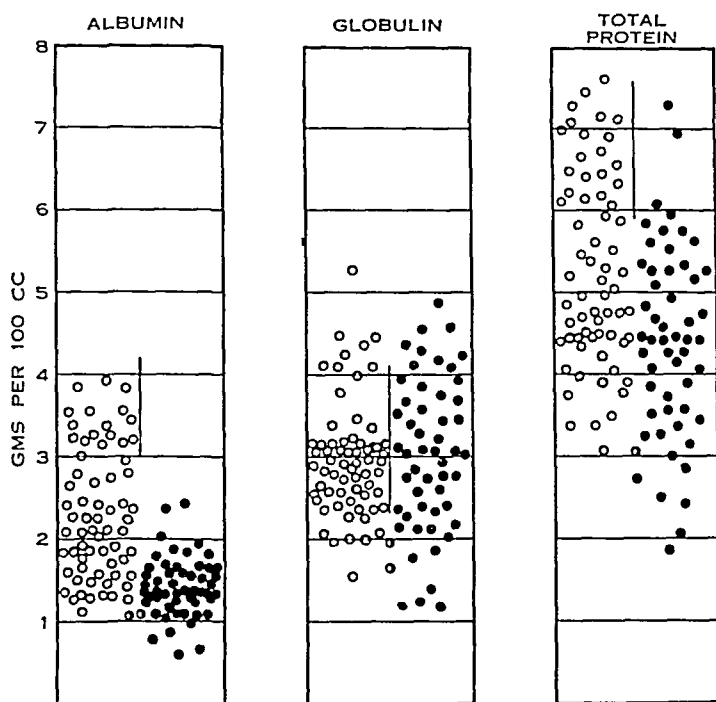


Chart 5—The relation between plasma protein concentration and edema in dogs. Open circles indicate estimations when no edema was present, black circles refer to determinations when edema was present, vertical lines in the middle of each column indicate the range of normal variation. From the *Journal of Clinical Investigation* 5

capillary because the capillary membrane is relatively impermeable to plasma protein while at the same time it is freely permeable to water, electrolytes, and other dissolved substances of low molecular weight. Under conditions where the capillary wall is damaged, the impermeability is destroyed and the edema which results represents simply the passage of plasma into the tissue spaces. Such forms of edema result from allergy and from inflammation. They need not concern us here. We must, however, be interested in the extent to which this protein traverses the wall of the capillary when there is no gross injury, that is, in defining as accurately as possible what we have called "relative impermeability." The available evidence is drawn from determinations of total protein in lymph<sup>26 27</sup> and in edema fluid. In view of Cecil Drinker's lecture<sup>2</sup> before this Society less than a year ago, I shall not discuss the subject of protein

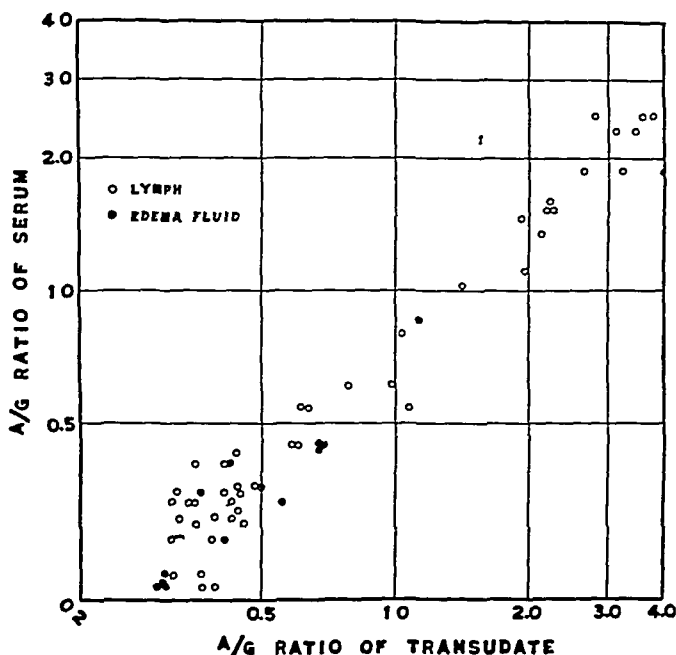


Chart 6—The relationship between the albumin globulin ratios of concurrently collected samples of serum and transudate. A logarithmic scale has been used to avoid crowding of the data in the lower left-hand corner of chart.

in lymph. Much information concerning the protein in edema fluid has been assembled by Peters.<sup>28</sup> In nephrosis the fluid contains very little protein, usually less than 0.1 gm per cent; in edema from myocardial failure the fluid contains more, generally from 0.5 to 2.0 gm per cent. With nutritional edema in man, data assembled in our laboratory<sup>16</sup> indicate that the protein content of subcutaneous edema fluid varies from 0.1 to 0.6 gm per cent. With experimental edema in dogs our experience is more extensive,<sup>25</sup> thirty samples from fourteen dogs have been examined. The range of protein concentration was from 0.02 to 0.72 gm per cent, the average level was 0.23 gm per cent and the median level was 0.17 gm per cent.

The data just cited are of great value in tracing the behavior of total protein in plasma as it flows through the capillaries; they do not help specifically in following the course of the albumin fraction. It has been suggested that albumin, because of its smaller molecular size, may diffuse

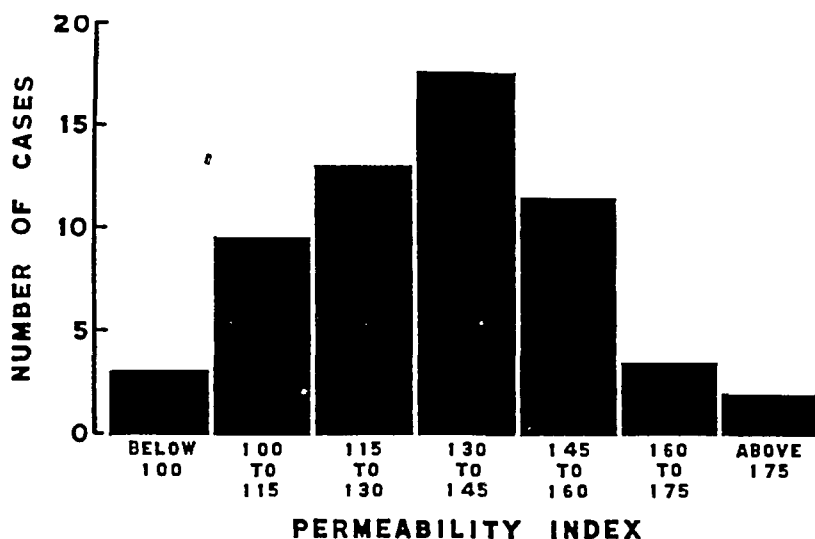


Chart 7

through the capillaries more freely than globulin and that the bulk of protein in edema fluid may be albumin. Because the osmotic pressure of albumin is much greater than that of globulin, it is desirable to have positive knowledge concerning the relative amounts of albumin and globulin in edema fluid. Information on this point has been supplied by Goettsch who in association with Kendall<sup>29</sup> developed a method for fractionating the serum proteins accurately in fluid samples of low protein content. The method is an outgrowth of fundamental work of Heidelberger and Kendall<sup>30</sup> and depends upon the precipitin reaction which appears when such fluids are brought into contact with specific rabbit antisera. Twelve samples of subcutaneous edema fluid and forty-eight samples of lymph from the extremities were obtained from normal and edematous dogs for this study, serum collected concurrently was also analyzed. Chart 6, prepared from these analyses, shows that the albumin globulin ratio of a transudate is related closely to the albumin globulin ratio of its corresponding serum. The concept is strongly supported that the albumin and globulin of lymph and edema fluid originate by filtration from the plasma. Incidentally it is shown that lymph and edema fluid are similar in this respect. In Chart 7 we have calculated for each transudate what may be called a "permeability index" and the indices have been arranged in the form of a frequency polygon. The index is secured when the A/G ratio of the transudate is divided by the A/G ratio of

the serum. When the permeability of the capillary is the same for albumin as it is for globulin, the index will have a value of one. As the index rises above unity a correspondingly greater differential permeability in favor of the smaller albumin molecule is indicated. The chart shows essentially a normal type of distribution for these permeability indices. The mode lies between 1.30 and 1.45, the average index is 1.35. The result tells us that albumin does traverse the capillary more readily than globulin but the difference is not extreme, if the ratio of albumin to globulin in serum is known the ratio in the transudate can be estimated by multiplying by 1.35. The chart shows three instances out of sixty in which the permeability index was less than one. I shall not attempt to explain these values other than to state that the figures were close to unity and that the slightly lower results may be merely an expression of analytical difficulties. They scarcely constitute grounds for believing that protein crosses the capillary wall by any other process than that of simple filtration.

Data of a similar nature for humans with edema are still meager. In seven cases where satisfactory analysis was possible the permeability indices ranged from 1.24 to 2.29 and averaged 1.55. There is little to suggest that in this respect the capillaries of the human do not behave like those of the dog. The reason why a larger number of analyses in the human is not available is part of another story which because of its importance can be touched on here. At the Babies Hospital most of the patients from whom adequate samples of edema fluid can be secured are children with nephrosis. It was while attempting to analyze samples from such patients that Dr. Goettsch<sup>31</sup> was led to discover that not only is the serum protein depleted in nephrosis but also that a part of the remaining protein is altered in a way which can be detected by the precipitin technic. This fact must become important in our ultimate understanding of the pathogenesis of nephrosis.

In addition to the data in Chart 7, three permeability indices have been determined for dog ascitic fluid. The values are 1.82, 1.98, and 2.18, all appreciably higher than the modal index for subcutaneous edema fluid and lymph. It will be recalled that fluid which leaves the blood to enter the subcutaneous tissue spaces must pass only one filtering layer of capillary endothelium, that which enters the abdominal cavity must in addition traverse the peritoneum. This fact may account for the higher indices recorded for ascitic fluid. If we suppose that capillary and peri-

toneum exert the same differential effect on filtration, a permeability index of 1.82 can be calculated for the two surfaces combined. The average of the three determined indices is 1.99.

I must now request a shift in the direction of your attention in order that we may consider another property of serum albumin, namely, that property which concerns its role in maintaining the volume of the blood. Not so many years ago the low concentration of protein in the serum of patients with nephrosis was interpreted to mean that both blood and tissues shared in the accumulation of edema, there was much talk of so-called "hydre-mic plethora." Probably Darrow,<sup>32</sup> 1926, was the first to record actual measurements which led to the conclusion that blood volume and plasma volume are below normal during the edematous stage of this disease. In view of contemporaneous work it is of interest that Darrow was able to reach his conclusion not on the basis of single measurements during the edematous phase but because volumes during edema and sometime after the disappearance of edema were compared. Other investigators<sup>33</sup> who studied the problem during this period, although able to dispose of the older concept of hydre-mic plethora, did not perceive the actual lowering in blood and plasma volumes. The findings of Darrow in nephrosis were later corroborated by Waterfield.<sup>34</sup> In 1932 Chang<sup>35</sup> in China in studying patients with nutritional edema found a close parallelism between blood volume and plasma protein. About the same time Lepore<sup>36</sup> made observations on dogs in the anemia colony of Whipple in Rochester, he found that the volume of the plasma varied consistently with changes in the concentration of albumin in the serum. Later, 1936, Melnick and Cowgill<sup>37</sup> reported that the parallelism between change in plasma volume and change in serum protein could be disturbed by significant alteration in the volume of red cells. You will see that we had been led to a similar conclusion.<sup>38</sup>

Chart 8 shows the average volume findings in ten of our dogs during maintenance on the low protein diet. Along with the decline in albumin which has already been described there is seen here to be a progressive fall in the total volume of the blood. The decline in red cell volume is likewise continuous but the plasma volume decreases for from twenty to thirty days only and thereafter remains at an approximately constant level. The failure of plasma volume to continue to fall does not mean that at this stage it is no longer sensitive to change in albumin concentration. In other experiments we have shown that at any degree of albumin

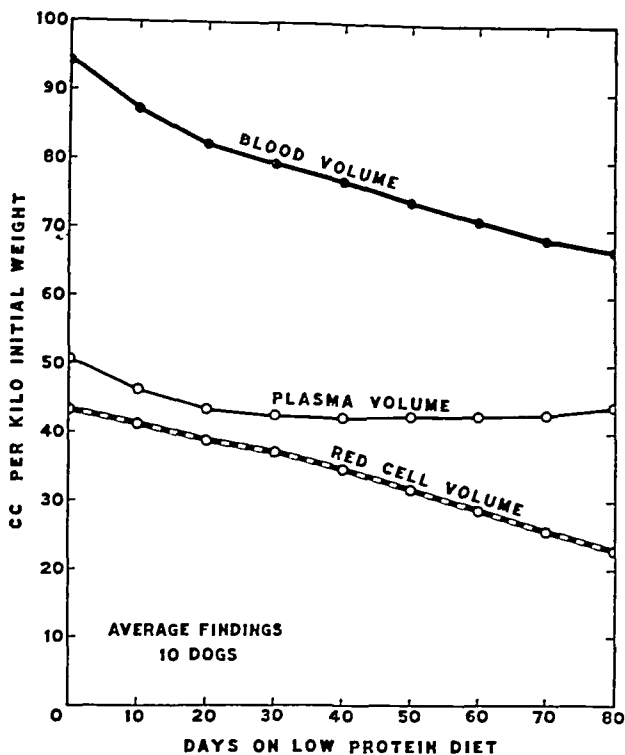


Chart 8—Changes in blood volume, plasma volume, and red cell volume during maintenance on the low protein diet. From the *Journal of Clinical Investigation* 38

depletion there will be an immediate rise in plasma volume if the albumin concentration is raised by transfusion either with serum or with solutions of serum albumin. We can imagine, however, that the continuous fall in blood volume which results from diminishing red cells has brought into play an opposing force strong enough to resist the effect of decreasing albumin concentration on plasma volume.

The fact that change in albumin concentration exerts an effect on the volume of the plasma assumes considerable importance when conditions are such that albumin is either rising or falling and it is desired to draw conclusions concerning some circulating substance from serial measurements of its concentration in blood. In Chart 8 it is seen that for some days the rate of decline is more rapid for plasma volume than

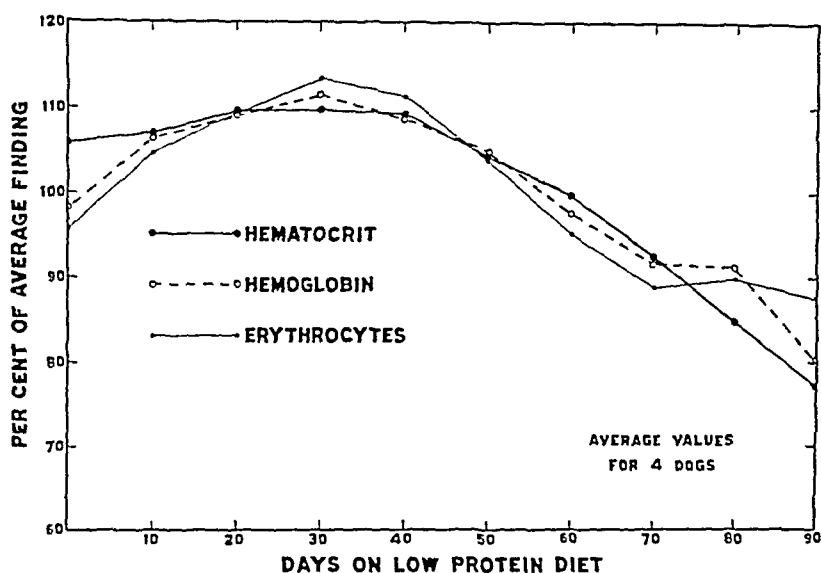


Chart 9—Variations in per cent cell volume, hemoglobin concentration, and number of erythrocytes during maintenance on the low protein diet From the *Journal of Clinical Investigation* 38

for cell volume. During this period then the concentration of red cells must rise even though the total quantity is falling. This paradox is brought out in Chart 9 which presents the usual type of hemoglobin, erythrocyte, and hematocrit measurements in four dogs during maintenance on the deficient diet. If such measurements only were available one might be led to the curious and incorrect conclusion that ingestion of a deficient diet has a temporarily beneficial effect on hemoglobin and erythrocytes. I may add that examples of the fallacy of such reasoning are easily found in the clinical records of patients for even as illness and anorexia tend to go hand in hand so also does failure of appetite associate itself with a fall in serum albumin.

### PART III

The physician who investigates disease need feel no shame if his labor brings understanding even though there be no relief for his patient. Nevertheless, he must ultimately be impelled by at least a desire to strengthen the armaments of therapy. With this thought in mind I shall now turn to a consideration of measures which are being devised to re-

lieve the symptoms of albumin depletion. Of such symptoms the most conspicuous is dropsy. It is therefore fitting that we should consider first the attempts to remove edema by injecting into the circulation either albumin, as contained in serum or blood, or a substitute for albumin, like gum acacia. As a preliminary caution, however, we should be reminded that the phenomenon of diuresis is complicated and that it depends more directly upon renal activity than upon any particular distribution of fluid between circulation and tissues. A complete explanation of the initiation of diuresis is therefore not given when we say that this or that procedure has raised the colloid osmotic pressure of the blood. Indeed, we are forced to this conclusion by the observation that diuresis with elimination of edema occurs not infrequently when no evidence can be found that the osmotic pressure of the protein in the circulation has been altered. In such cases slight rises in albumin concentration in the plasma are often better interpreted as signs of blood concentration resulting from the diuresis than as the cause of its inception. In this connection I should like you to entertain a thought concerning the possible sequence of events when transfusions with serum, with blood, or with acacia are successful in initiating a diuresis. Experience indicates that these procedures, even when successful, usually produce slight and sometimes negligible effects on osmotic pressure. The evidence is strong, however, for an abrupt rise in plasma volume. It may well be that the rise in plasma volume is associated with an increase in renal blood flow and that the latter is responsible for stimulating kidney activity. In any case the possibility that some such sequence of events is involved will help in our understanding of observations that have been made in the clinic and in the laboratory.

Transfusions with blood to replenish the serum albumin have been attempted in many places. I know of no tabulation which permits appraisal of the efficacy of the procedure. Reports have appeared of cases in which the measure was successful in initiating diuresis but failure to obtain such action is a more common experience. Transfusions with serum alone have undoubtedly been used from time to time even as we at the Babies Hospital have occasionally turned to this procedure. Reports indicating conspicuous success have not appeared. Probably because the method involves the labor of handling large volumes of blood and because in many instances the blood must be purchased the attention of investigators has been directed along other lines.



In 1932 Hartmann and his colleagues<sup>39</sup> in St. Louis suggested the use of acacia as a substitute for serum albumin in raising the osmotic pressure of plasma. By injecting this gum in large amounts intravenously Hartmann was successful in initiating diuresis in five out of six patients with nephrosis. Our own experience with this procedure has not been so rewarding, because severe constitutional reactions were encountered in the first few patients, we have not encouraged its use. Moreover, it has been reported<sup>40</sup> that much of the injected acacia is ultimately deposited in organs throughout the body, particularly in the liver, and Dick and his associates<sup>41</sup> have observed clinically that the continued use of acacia depresses still further the already depleted serum protein and is associated with an enlarged tender liver. Under such circumstances it is probably fair to assume that the procedure will not become popular even though its occasional use may be justified.

During the past summer a report has appeared of a more promising method of combatting serum albumin deficiency. Aldrich, Stokes, and other associates<sup>42</sup> have described a diuretic effect in nephrosis from injections of concentrated human blood serum. The serum used had been preserved in dried form by the lyophile process and was injected after redissolving so as to yield fourfold or fivefold concentration. In six of nine patients treatment was followed by complete and immediate diuresis. The authors did not feel, and indeed their analyses scarcely indicate, that the favorable results were due entirely to the osmotic action of the lyophile serum. They suggested that in addition some substance had been supplied which set off the patients' own mechanism of diuresis. Systemic reactions to the serum were usually mild but in two instances chills and high fever were seen. Dr. Lyttle has had some experience with this procedure at the Babies Hospital. Four children with nephrosis have been treated and in two of these the more severe type of reaction with chills and fever was noted. In only one case was satisfactory diuresis elicited. We were likewise led to conclude that the effect could not be ascribed to elevation of serum albumin concentration, but a sharp fall in the hematocrit reading following each injection suggested that the procedure did increase the plasma volume.

Because this form of treatment is destined to receive extensive trial in the near future it may be helpful to review one of a series of experiments performed several years ago<sup>43</sup> in which nutritional edema in the dog was treated by a similar method. Dog 2-07, Chart 10, had received

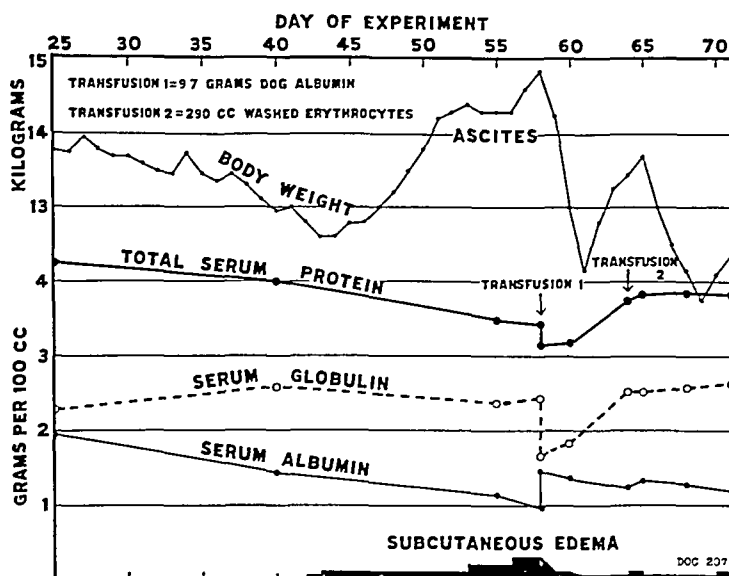


Chart 10—The effect of transfusion on serum proteins and edema in nutritional edema in a dog

the low protein diet for fifty-eight days before treatment by transfusion was tried. The serum albumin had declined to less than 1 per cent and ascites had developed. At this point the animal was given intravenously 38 cc of a 25.4 per cent solution of dog serum albumin. Before injection the plasma volume was measured and the total albumin in the circulation estimated to be 6.3 gm. The amount of albumin injected was 9.7 gm. The reaction was mild but similar in type to that observed in other dogs which have exhibited chills, diarrhea, and rapid irregular pulse of low volume. The subsequent clinical effect of diuresis which continued for three days was most encouraging. The changes in serum protein concentration are shown on the chart, a rise in albumin of only 0.5 gm per cent and a fall in globulin great enough to produce an actual lowering in total protein. These changes were associated with a sharp fall in the hematocrit reading. Separate calculations based both upon the fall in hematocrit and upon the alteration in albumin indicate that the transfusion was followed by an abrupt increase in plasma volume from 630 to about 1,080 cc. We suspect that the reaction of shock may depend upon the sudden demand on cardiac reserve consequent upon such in-

creases in blood volume. The change in protein concentration in the serum is scarcely an adequate explanation for the degree of diuresis which ensued. Some light may be shed on this point by subsequent events. After the three-day diuresis the body weight again rose as edema reaccumulated. On the sixty-fifth day a second transfusion was given with 290 cc of erythrocytes which had been washed in saline to remove the plasma. This time there was no untoward reaction and no demonstrable change in the serum proteins. Nevertheless, diuresis which lasted for four days was again instituted. The large volume of transfused red cells must have increased the total blood volume and this circumstance may have stimulated the kidney to diuresis.

If any conclusion is to be drawn from experiments of this type, it is that red cells and serum may both have some value in treatment. Transfusions with serum are invariably followed by a fall in relative cell volume and it would seem the part of wisdom to administer enough whole blood to prevent the fall. If it is true that untoward reactions may result from sudden increase in plasma volume, small and frequently repeated, rather than large, transfusions are indicated.

The futility of attempting to transfuse enough serum to replenish entirely the deficits in disease has been impressed on all who have tried the procedure. Albumin depletion is invariably a sign that the stores of nitrogen in many tissues are likewise depleted and it may be impossible to prevent an exchange of protein between circulation and other tissues when large volumes of serum are injected. Whipple and his associates<sup>44</sup> have already indicated the possibility of such an exchange by demonstrating in the dog that the protein requirement of the entire body can be met by massive transfusions of plasma. The only practical way in the clinic of meeting the full demand of the body for protein is through the diet.

From time to time and in different places the idea has evolved that some dietary proteins may be more efficient than others in supplying the needs of the plasma. There is opportunity merely to mention the convincing and provocative work of Whipple<sup>45</sup> who with his associates has utilized the technic of plasmapheresis to show that qualitative differences exist among different foods with respect to their utilization in forming serum protein. The remaining portion of this lecture must be devoted to experiments having a similar purpose now under way in our own laboratory<sup>11, 46</sup>. These experiments have as their ultimate goal the

classification of the more important food proteins with respect to their ability to promote the formation of serum albumin

The method which is being used to assay the food proteins is simple. A healthy dog is selected and placed under daily observation for six days on a standard diet of adequate protein content. The standard diet is a mixture of 900 grams of our basal low protein ration with 90 grams of casein. The concentration of albumin in the serum is then measured, the casein is removed from the diet and the period of depletion of the serum albumin is begun. After three weeks the serum albumin is again determined and the period of regeneration started on a diet composed of a mixture of the basal diet and the food protein to be tested. The mixture is fed at an energy level of eighty calories per kilo and at a protein level of 2.5 grams per kilo. After one week on this diet the final measurement of serum albumin concentration is made.

The initial albumin analysis is a control determination only, the result has no direct part in evaluating the assay. The difference between the third and the second analyses gives the rise in serum albumin concentration during the week when the test protein was fed. In twenty-three control experiments in which the basal low protein diet was actually fed longer than three weeks, the average decline in albumin during the fourth week was 0.15 gm per cent. Since the test food should receive credit for preventing this decline, the "assay value" is calculated as the rise in albumin concentration plus 0.15. When assay values are determined for the same food on a number of different animals, the range of biological variation among the results will be fairly wide. It follows that a series of assays must be made before an average value, called "the potency value," can safely be assigned to any one protein.

Table III shows the results of twelve assays of casein by this method. The columns in the table show the albumin levels at the start of each experiment, the levels reached at the end of three weeks of low protein feeding, and the final levels attained after one week when casein was again incorporated in the diet. In the next two columns the loss in concentration during the period of depletion is compared with the subsequent gain. The assay values are obtained by adding the maintenance allowance, 0.15, to the figures which represent gains in grams per cent. The potency value or average of the assay values is 0.388. Although the majority of the assay values are in fairly good agreement with the potency value, I must direct your attention to the extreme variability in

TABLE III  
ASSAYS OF CASEIN FOR ALBUMIN FORMATION

Dog	Initial	Serum Depletion	Albumin per 100 cc Regeneration	Loss	Gain	ASSAY VALUE
	gram	gram	gram	gram	gram	
B-12	3.81	2.63	2.55	1.18	-.08	0.07
5-7	3.61	2.76	2.79	0.85	0.03	0.18
5-31	4.07	3.04	3.25	1.03	0.21	0.36
7-27	3.40	2.27	2.51	1.13	0.24	0.39
6-35	2.89	1.90	2.11	0.99	0.24	0.39
8-04	3.38	2.52	2.77	0.86	0.25	0.40
9-51	3.46	2.73	2.99	0.73	0.26	0.41
7-28	3.16	2.40	2.70	0.76	0.30	0.45
7-47	3.44	2.47	2.78	0.97	0.31	0.46
3-0	3.80	2.91	3.23	0.89	0.32	0.47
9-49	1.60	3.20	3.54	1.40	0.34	0.49
3-36	3.12	2.66	3.09	0.76	0.43	0.58

POTENCY VALUE  $0.388 \pm 0.027$  (P.E.)

From the *Bulletin of the Johns Hopkins Hospital* 11

TABLE IV  
ASSAYS OF BEEF SERUM FOR ALBUMIN FORMATION

Dog	Initial	Serum Depletion	Albumin per 100 cc Regeneration	Loss	Gain	ASSAY VALUE
	gram	gram	gram	gram	gram	
1-68*	3.39	2.61	2.80	0.78	0.19	0.42
5-31	4.14	3.23	3.66	0.91	0.43	0.58
3-0	3.69	2.83	3.28	0.86	0.45	0.60
7-31	3.58	2.53	3.02	1.05	0.49	0.64
9-51	3.47	2.59	3.10	0.88	0.51	0.66
2-05*	3.63	2.29	2.71	1.34	0.42	0.74
6-35	3.26	2.42	3.11	0.84	0.69	0.84
9-52	2.61	1.45	2.20	1.16	0.75	0.90
3-36	3.72	2.74	3.63	0.98	0.89	1.04
1-69*	3.02	2.19	2.88	0.83	0.69	1.12
1-55	3.61	2.39	3.51	1.22	1.12	1.27

POTENCY VALUE  $0.801 \pm 0.053$  (P.E.)

\* In these experiments the regeneration period lasted for five instead of seven days. Calculation of the assay values is explained in the original publications. From the *Bulletin of the Johns Hopkins Hospital* 16

a few experiments, the extreme cases give a total range among the assay values from 0.07 to 0.58. This tendency for a few animals to diverge widely from average behavior constitutes the major difficulty encountered in experiments of this type. So far we have not learned how to overcome the difficulty except by performing a fairly large number of assays with each food.

Table IV shows the results with the most potent food protein we

TABLE V

	<i>Gelatin</i>	<i>Casein</i>	<i>Beef Liver</i>	<i>Beef Chuck</i>	<i>Egg White</i>
Beef Serum (11) 0 801	0 0001	0 0001	0 0003	0 0007	0 042
Egg White (11) 0 613	0 0001	0 0003	0 0026	0 0090	
Beef Chuck (12) 0 475	0 0001	0 098	0 42		
Beef Liver (12) 0 436	0 0001	0 38			
Casein (12) 0 388	0 0001				
Gelatin (4) - 093					

have tested so far, namely, beef serum. Eleven assays have been performed. Only the two lowest assay values overlap with the casein series. The remaining values are higher than any recorded with casein. The potency value for beef serum, 0 801, is more than twice that for casein.

At the present time assays of six foods have been completed. The values for the six foods arranged in order of potency are given in the left-hand column of Table V. Beef serum is first, with a potency value of 0 801. It is significant that Whipple came to the same conclusion by a wholly different method of assay. There follow egg white (11 assays), 0 613, beef muscle (12 assays), 0 475, beef liver (12 assays), 0 436, casein (12 assays), 0 388, gelatin (4 assays), -0 093. In three of the four assays of gelatin, the albumin level at the end of a week of feeding this protein was less than would have been expected if no protein at all had been fed.

Gelatin therefore appears in the table with a negative value. The remaining columns of the table are given over to a statistical tabulation of the probability that the difference in potency value between any two of the foods is significant. When the tabulated value of the probability integral is less than 0.05, a significant difference may be regarded as established. Beef serum is clearly more potent than casein, beef liver, and beef muscle, the difference between beef serum and egg white is barely significant. Egg white, however, is secure in second place. There is no question concerning the absolute inferiority of gelatin. However, a real difference between beef muscle, beef liver, and casein has not been shown.

The clinical usefulness of assays of this kind remains to be demonstrated. Because physicians have sometimes failed to observe startling distinctions among different food proteins in humans with nephrosis does not mean that qualitative differences such as we have shown to hold for the dog do not also apply in man. The suggestion has already been made that in disease the replenishment of albumin may sometimes be delayed by injury of the organ concerned in synthesis. Such injury when present will complicate greatly the interpretation of dietary experiments on the ward.

\* \* \* \* \*

In summary I have traced for you some of the features which characterize the behavior of the albumin fraction of serum, the manner in which it becomes depleted when dietary protein is inadequate and the path of regeneration when adequate feeding is resumed. I have discussed the part in physiology served by albumin by virtue of the osmotic pressure which it exerts, namely, its function in protecting the circulation as blood flows through the capillaries so as to prevent edema and its role in maintaining the volume of the blood. And finally, I have described experiments which look toward the more intelligent management of patients who suffer from depletion of serum albumin.

In conclusion. The material from which this Harvey Lecture was composed was chosen to trace the course of research in a single experimental laboratory. You have honored me in asking that I tell the results of the work, and in turn it becomes my privilege to divide the honor with those who have gone with me with Dr. Elvira Goettsch who has been my associate for the past seven years, with several technicians who have endured the tedium of thousands of Kjeldahl analyses,

with Boris Gagarin who with devotion has cared for my dogs, and finally with all of those friends and associates at the Medical Center who by conversation and suggestion have been responsible for crystallizing the ideas which have been expressed

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## GENERAL PATHOLOGY OF LYMPHOSARCOMA\*

JAMES EWING

WHEN all forms of primary tumors of lymph nodes are combined, the total incidence of this group of diseases becomes quite formidable. A search for statistical data brings to light the notable fact that there are no reliable data on this subject and also that in the present state of knowledge and the attitude of the medical public mind, there is no possibility of obtaining them. The United States Census of 1934 reports 1,512 deaths from pseudoleukemia and Hodgkin's disease, and 3,403 from the leukemias, while the majority of cases of fatal tumors of lymph nodes are classed under cancer of lymph nodes, from which it is impossible to determine how many were primary in the lymphatic system. It is well known that lymphatic diseases are more common in the Orient, and in Batavia, Java, the lymphosarcoma group ranks fourth on the list of deaths from cancer. From this state of affairs, one obtains support for the impression that lymphosarcoma, although a major medical problem, is a badly neglected field of observation, and that until some efforts are made to bring order into this chaos, beginning with nomenclature, little accurate information regarding the economic and social significance of this disease will be available. All that we know is that lymphosarcoma is a relatively common disease, nearly always fatal, of quite obscure etiology and pathology, generally difficult of diagnosis, and little influenced by treatment. All these facts were well known to Paltauf and Kundrat fifty years ago.

Etiological data being largely lacking, we are still compelled to rely upon morphology for the classification of tumors of lymph nodes. Applying this principle, three main structural varieties of these tumors are clearly distinguishable: lymphadenoma, lymphocytoma, and reticulum cell lymphosarcoma. Each of these varieties is associated with rather typical clinical characters and each is doubtless referable to specific etiological factors as yet undetermined. A simple scheme shows how specific structure goes with peculiar clinical course.

\* Delivered November 1, 1938, in the Eleventh Annual Graduate Fortnight.

*Lymphadenoma*

Multiple giant follicular lymphadenoma—Brill's disease  
Gastrointestinal pseudoleukemia

*Lymphocytoma*

Systemic pseudoleukemia  
Lymphocytic leukemia  
Malignant disseminating lymphocytoma  
Plasmacytoma  
Solitary lymphoma

*Reticulum Cell Lymphosarcoma* Large round cell lymphosarcoma affecting many regions and organs

The term lymphadenoma is appropriate because the lymph node is an organ and the lesion reproduces all the features of the organ in more or less orderly fashion but with varying grades of anaplasia and malignancy. In lymphocytoma the cell affected is the lymphocyte, while reticulum cells are passive. All grades of malignancy are observed. It is surprising how tardy has been the recognition of the specific features of reticulum cell lymphosarcoma. The most superficial comparison of the structure of a series of lymphatic tumors reveals the sharp distinctions between the small cell lymphocytic and the large reticulum cell sarcomas.

The early observers including Paltauf did not attempt fine distinctions between the different tumors of lymph nodes, but they fully recognized the two main varieties, small and large cell. Thirty years ago I began to point out to students the histogenesis of the two types of tumors of lymph nodes, and in 1913 in an article on endothelioma of lymph nodes, I discussed this subject in detail, supposing that it was so widely recognized among pathologists as to require little emphasis. Yet it was not until 1932 that an article by Roulet, proposing the term of reticulum cell lymphosarcoma, brought this term into general use. Ringertz of Stockholm has recently reviewed this history in detail.

A sketch of the main features of characteristic cases of the three varieties of lymphatic tumors may serve to emphasize their specific nature.

*Lymphadenoma* Multiple giant follicular lymphadenoma is a systemic disease, usually widely generalized when first observed, affecting many or all groups of lymph nodes and the spleen, associated with rather moderate anemia, weakness, occasional mild pyrexia, running a progressive course, favorably affected by radiation but recurring with increasing severity and generally proving fatal in five to ten years. The tumors

are not large and there is a limited scope of malignancy, but certain cases develop somewhat aggressive tendencies toward the terminal periods. Etiological factors are practically unknown. The structure shows a remarkable predominance and persistence of large, well-formed lymph follicles, with hyperplastic germ centers, with excess of lymphocytes of mainly normal type. In a few cases more diffuse growth may appear and the structure of diffuse lymphosarcoma may be produced.

Gastrointestinal pseudoleukemia is a term designating a very peculiar systemic disease affecting at times the entire gastrointestinal tract, producing myriads of small lymphomas in the mucosa from mouth to anus, without ulceration, and extending to many chains of lymph nodes and spleen, running a steadily progressive and rather active course with some fever, anemia, diarrhea, emaciation, peritonitis, and death within a few years or few months. The structure shows a remarkable tendency to be limited to the growth of many rather well-formed lymph follicles composed of normal or large lymphocytes and few reticulum cells, but lacking the diffuse growth of a malignant tumor or the ordinary type of systemic pseudoleukemia. Etiological factors are entirely unknown. I see nothing gained by merging these specific clinical entities with the general group of lymphosarcoma or pseudoleukemia, while the structural features are accurately indicated by the term lymphadenoma.

*Lymphocytoma* covers a wide field of clinical conditions and an equally varied morphology, determined mainly by the grade of malignancy and doubtless by the still undetermined etiology of most of its forms. At one end of the series stands the simple solitary lymphoma, a benign tumor composed of a diffuse growth of lymphocytes, occurring in many organs, often reaching a large size, and not recurring after operation or radiation. The average case of systemic chronic pseudoleukemia presents the structure of simple diffuse lymphocytoma. In many such cases a tuberculous etiology is well established. Lymphatic leukemia belongs in this group of lesions. The malignant forms of lymphocytoma present features which distinguish them from other types of lymphosarcoma, particularly from the reticulum cell sarcomas. Billroth's malignant lymphoma was the classic example of the older writers. This disease begins as a localized tumor of one node or chain, rapidly progressing, fusing the nodes, infiltrating the surrounding tissues and producing widespread metastases, generally aggravated by operation, now known to resist control by radiation or prone to recur, and

probably always fatal, with fever, anemia, and cachexia. The pathologist recognizes the terminal stages of malignant lymphocytoma by the widespread metastases, especially in serous membranes and in tissues not normally containing lymphatic tissue, and by the production of many, even myriads, of small lymphomas. The clinician may find little satisfaction in attempting to recognize distinctions between lymphatic disease before which he stands mainly a helpless observer. Intermediate grades of malignancy of lymphocytoma are found among the numerous cases of pseudoleukemia and lymphatic leukemia. That some of the very malignant forms represent terminal stages of the less malignant is illustrated in any broad clinical experience. On the other hand there are obvious differences between the most rapid lymphatic leukemia and the highly malignant lymphocytoma without leukemia. I recall a case of acute febrile lymphatic leukemia lasting eighteen days, with 600,000 leukocytes in the blood and widespread miliary lymphomas in the organs, but the lymphomas failed to affect the serous membranes, were never infiltrative, and exerted only mild pressure effects, whereas in the malignant tumor the lymphomas were universal, destructive, and produced aggressive tumors.

*Reticulum Cell Sarcoma* covers the main field of the lymphosarcomas and includes the great majority of the cases. The classical description of the older writers deserves repetition. The disease begins in a chain of nodes or in a localized area of a mucous membrane. All the nodes of the chain are affected from the first. The disease spreads by involving other chains of nodes but generally the whole new chain appears enlarged. The method of extension is obscure but probably involves both dissemination of the exciting agent and cell embolism. Isolated bulky metastases appear both in the lymphatic system and in other organs in which the new tumors arise in tissues entirely free from other signs of lymphatic irritation. Yet the primary focus is generally discernible at autopsy and appears to dominate the course of the disease. Hence early excision or radiation of the primary lesion has often controlled the disease. The clinical varieties and manifestations of reticulum cell sarcoma are extremely numerous, affecting every organ and tissue, obtruding themselves into every medical specialty, and at all ages.

Out of this complex clinical field certain generalizations stand out prominently. There is the very notable healthy robust overnourished appearance of the average subject of reticulum cell sarcoma, which is

sharply contrasted with most other forms of lymphatic diseases and especially with Hodgkin's disease. There is the tendency to localization, at least temporary, of the primary lesion. There is the tendency to limitation to the organ in which the disease arises, especially noted in lymphosarcoma of skin, spleen and bone marrow. There are rather specific cellular features detectable in lymphosarcoma of spleen, thymus, stomach, and some other organs, on which a localizing diagnosis may often be made. There is a notable frequency for the disease to terminate with streptococcus septicemia. A gloomy generalization relates to the highly lethal prognosis of this lesion in any form, so that one is compelled to regard with gravity the appearance of any spontaneous enlargement of a chain of lymph nodes, especially in an adult.

While the chief structural feature is simple enough, consisting in a diffuse growth of reticulum cells of varying degrees of anaplasia, there is a surprising variety in structural details which render the exact diagnosis and prognosis of lymphosarcoma one of the most difficult tests of the pathologist. It is seldom possible to predict whether the patient will live a few months or several years. Addicts to histological refinements point out certain peculiarities of structure, like Albertoni, who notes the lesser malignancy of tumors in which there are many large clear cells. The experienced pathologist contents himself with recognizing two main classes of structure in large cell lymphosarcoma, one being difficult to separate from a cellular infectious granuloma, while at the other extreme, one places the highly atypical diffusely growing process without any trace of granuloma. A fine intercellular argentophile reticulum is a characteristic structural feature.

In a serious effort to sharpen the diagnostic skill of pathologists, a Registry of Lymphatic Tumors was established at the Army Medical Museum some years ago. It makes progress slowly, chiefly because of the long period of observation required to complete the records, but now contains about 400 cases. It is a valuable mine of observation and opportunity for the student and deserves the hearty support of clinicians and pathologists, but it suffers from the general neglect visited upon the whole subject of lymphosarcoma and is seldom consulted. In this collection, the three classes of lymphatic tumors are fully illustrated and the diagnostic problems sharply emphasized. These problems consist chiefly in the distinctions between simple inflammatory and granulomatous inflammation, between tuberculosis and Hodgkin's disease, the

separation between inflammatory and neoplastic processes, and the recognition of grades of malignancy. All these problems constantly confront the pathologist and they are so difficult that one often wonders whether any adequate classification of lymphatic diseases is possible in the present state of knowledge.

The position of the leukemias in the scheme of lymphatic diseases is not easily determined, and is not adequately covered in the above groups which deal only with true primary tumors. Present knowledge indicates that the leukemic blood picture is a symptom arising under many different conditions and from a wide variety of etiological factors. Some of these processes are purely inflammatory and even transitory, others seem more or less autonomous, irreversible, and neoplastic, while in still others the underlying process is one of the many recognized varieties of malignant tumors of lymph nodes. On the ground that the leukemias are primary diseases of the bone marrow they might be excluded from the class of primary diseases of the lymphatic system. Yet it is unsafe to press this principle too far and for practical reasons the leukemias should be included in the general group of lymphomas. To cover the leukemias and certain other rarer forms of lymphatic disease, it is necessary to expand the classification and add to the three main classes of tumors certain subvarieties. Lymphatic leukemia falls with pseudoleukemia under lymphocytoma. Myelocytic leukemia is a specific process in which granular myelocytes are found in the hyperplastic nodes. Plasma cell leukemia, lymphomas, and lymphadenitis also stand out by themselves.

*Endothelioma of lymph nodes.* The doctrine that there is a specific group of primary tumors of lymph nodes, derived from the lining endothelium of cavernous and lymph sinuses, producing a structure resembling carcinoma, has been nearly wrecked by the discovery by Regaud and Schmincke of lymphoepithelioma. Probably the great majority of tumors recorded as endothelioma of lymph nodes were derived from the lining epithelium of mucous surfaces in which lymphatic tissue is abundant, as in the nasopharynx. Nevertheless the literature continues to supply rather frequent examples of tumors presenting the rather characteristic structure which the authors derive from lining endothelial cells. In many of these cases a clinical search or postmortem examination, which is stated to be thorough, fails to reveal any primary focus in the mucous membranes. I continue to see occasional cases submitted in which these conditions are asserted to exist and the structure



of the tumor and its clinical course are peculiar. In my own material I have not seen in recent years, any cases of this type in which a primary focus was positively excluded. While unable to deny that a primary endothelioma derived from sinus endothelium exists, I am inclined to think that cases of this type will diminish in frequency as observations become more precise and critical.

*Etiology* An attempt to review the clinical data regarding the causation of lymphosarcoma is like looking into a fog at sea, and this impression is aggravated by inspection of current literature. Present day studies are wrestling with morphology, and there is little systematic effort to elucidate the problems of etiology. It is evident that lymphatic hyperplasia and neoplasia may be excited by a great variety of conditions which include every class of external irritant, supported by many contributing factors and favored by certain predisposing causes.

Subacute bacterial infection stands as one of the common excitants of lymphatic tumors, especially of skin and mucous membranes in man and lower animals. The pyogenic cocci, especially the group of streptococci, are most prominent in this relation, but many other microorganisms seem to be concerned in special cases. That subacute streptococcus infection is capable of producing lymphocytic and reticulum cell hyperplasia instead of polynuclear leukocytic exudate, was established long ago. In the skin, staphylococcus, ringworm, and many other common skin infections have been observed to precede lymphomatosis. A careful search for old or recent infections of skin and mucous membranes in cases of lymphosarcoma of these or deeper organs is rewarded with success in a large proportion of such cases and should always be undertaken. It is not an uncommon history that the patient suffered some months or years previously with a local infection accompanied by enlargement of regional nodes which subsided, but after a variable period the lymphatic enlargement returned in the form of lymphosarcoma. In a group of cases of deep lymphosarcoma, there is a history of typhoid fever, appendicitis, cholecystitis, salpingitis, or other local infection for which medical attention was required.

Most prominent among the established causes of lymphosarcoma are the infectious granulomas, including probably all of them, but especially tuberculosis and Hodgkin's disease. Tuberculosis is the chief causative agent in the entire group of lymphocytomas, but its relation to reticulum cell tumors is less definite. The transformation of a hyperplastic tubercu-

lous process into lymphocytoma has been observed many times, and the existence of a tuberculous process in such cases has probably often been overlooked. It has long been known that tuberculous infection with or without many tubercle bacilli may take the form of a nearly pure lymphocytic hyperplasia. In many cases of systemic pseudoleukemia, definite foci of tuberculosis may be found at autopsy.

The scope of morphology of Hodgkin's granuloma is so wide and its causative agent so uncertain that no definite statement may be made regarding its relation to lymphosarcoma. Hodgkin's granuloma affects reticulum cells more than lymphocytes, and one may assume that any lymphosarcomatous process arising on the basis of Hodgkin's disease would take the form of reticulum cell sarcoma. In typical cases of Hodgkin's disease, sarcomatous features may develop, involving the reticulum cells, but the process does not greatly resemble the typical reticulum cell sarcoma. That Hodgkin's disease ever takes the form of a true malignant neoplasm has never been proven, but it may be that certain cases of reticulum cell sarcoma arise on the basis of a Hodgkin's infection. Hodgkin's is the most typical of all the infectious granulomas, and the rather popular theory of its essential neoplastic character is without foundation.

An important relation of syphilis to any of the primary tumors of lymph nodes is not supported by very substantial data. Several less common infectious granulomas should probably receive more attention as possible causes of lymphomas. *Micrococcus melitensis* and venereal lymphogranuloma produce lesions closely resembling some of the atypical lymphomas, and subinfections by these agents may be concerned with some of the lymphosarcomas.

In the gastrointestinal tract, granulomas of undetermined origin affect stomach, bowel, appendix, and rectum, and produce lesions which greatly resemble in most respects the fully developed lymphosarcomas of these regions. Through such portals of entry the deep thoracic and abdominal nodes are probably infected. In all cases of retroperitoneal lymphosarcoma, the gastrointestinal tract should be carefully searched for healed or small active lesions.

Constitutional factors seem to play a prominent part in the causation of the typical cases of reticulum cell sarcoma. This disease is remarkable for its predilection for robust, over-nourished, florid types of individuals who maintain their euphoria nearly to the terminal periods. Most of the

cases of Brill's disease also occur in such subjects. Veterinarians are quite familiar with the frequency of lymphosarcoma in cattle bred for the market, for hundreds of such animals are condemned every year for lymphomatosis. The nature of the predisposition established in such subjects is at present wholly obscure.

Experimental cancer research has brought out some peculiar etiological factors, the relation of which to human disease is quite uncertain. In mice, leukemia is produced by inoculation of cells and some strains are susceptible, others refractory. Leukemia has been produced experimentally in fowl by cell free extracts (Furth), by extracts of normal organs (Schridde), by benzol (Bungeler), and by radiation by radium or x-rays. Occasionally, leukemic or lymphomatous processes arise after the application of the cancerigenic cyclic compounds.

*Criteria of Lymphatic Tumors* In the interpretation of lymphatic tumors, certain special criteria must be considered. Lymphatic tissue is present in nearly all tissues of the body and the total amount of this tissue is quite large. Lymph nodes are not fixed organs but come and go, varying in different species of animals, at different ages, in individuals, and in response to changing physiological conditions. The lymph node is the first barrier against infection which has passed the skin or mucous membrane, and the lymphocyte responds to irritation more readily than any other cell except the polynuclear leukocyte. The scope of reversible inflammatory hyperplasia is very wide and the existence of an irreversible neoplastic hyperplasia should not be assumed unless the autonomous characters are pronounced. There are physiological distinctions between systemic, thymic, and splenic cells and these often are traceable in tumors of these organs. There are free connections within the lymphatic system and with the blood vessels which render lymphatic tissue more or less mobile. This relation probably accounts for the tendency of lymphatic diseases to become systemic. It renders difficult the interpretation of metastases. There are indications that the extension of lymphatic tumors proceeds chiefly by cell embolism, but often by the development of new tumor cells by diffusion of the exciting agent. The possibility exists that growth stimulating cell products diffusing from the primary tumor focus may play a part in the remarkably wide and rapid extension of some lymphatic tumors. At times the whole lymphatic system seems to react as a whole.

There is a remarkable relation between lymphocyte and reticulum

cell most obvious in the follicles Flemming's theory that the reticulum cells of the germ center are the mother cells of lymphocytes has been abandoned, for embryological and pathological data point strongly to the view that these two types of cells are distinct. In most pathological processes this distinction is rigidly maintained, but it cannot be denied that in some pathological conditions the two types of cells seem to grow together and the usual sharp distinctions are obliterated. The lymphocyte may reach considerable dimensions, while in some very active reticulum cell sarcomas, the cells may be rather small. Yet I have never seen any definite evidence of the existence of a mixed lymphocytic and reticulum cell sarcoma. The reticulum of reticulum cell sarcoma is usually prominent in this process while regularly absent in all stages of lymphocytoma. The growth of reticulum may account for the tendency to fibrosis observed in many reticulum cell tumors. Necrosis is notably lacking in both classes of lymphatic tumors. The failure of the lymphocyte to provide immunity against the infecting agent is a remarkable feature lacking explanation. This failure may be held responsible for the lethal character, however delayed it may be, of most lymphatic tumors and its granulomas. When enlarged lymph nodes appear anywhere in a subject after puberty, the outlook is always serious.

For many years pathologists have expressed the feeling that lymphosarcomas are not true tumors but require separate positions among pathological processes. They find that this process is so intimately connected with and dependent upon infection or extrinsic irritation, and presents so many features of an inflammatory process, that it may not be given a definite place among strictly autonomous neoplasms. This fact should be noted by workers with various so-called tumors among lower animals.

The foregoing sketch of the problems of lymphosarcoma impresses the critical observer mainly with the fragmentary character of our knowledge of this group of diseases. Every pathologist will admit that when faced with the simple question of diagnosis he has as a rule to be content with a vague report on the general morphology of the process but can offer little help regarding etiology, and must rely for prognosis on the generally fatal tendency of the disease. Regarding essential factors controlling the origin and progress of the disease he must confess nearly complete ignorance. The clinician records the various incidents marking the course of the disease but must acknowledge his inability

to alter the course except temporarily in the great majority of cases. His inquiry into etiological questions is handicapped by the absence of definite leads from the pathological side. The therapeutics of lymphosarcoma, although considerably encouraged by the occasional recoveries after radiation, is a gloomy chapter. The comparative frequency of these lymphatic diseases, and their occurrence in apparently healthy subjects of all ages, most of whom die in spite of all efforts, discourages optimistic attempts to improve the situation by clinical resources. Recognition of these outstanding facts has led to the establishment of at least one Foundation directed to the systematic study of one group of cases, the leukemias, while tragedies in many families have occasionally led to the granting of small sums to support of isolated workers. While the leukemias have been systematically pursued by experimental workers in several localities under the Tata Foundation, most of the work is undertaken by individuals who take up phases of the subject, pursue them for a time, and then become discouraged by the paucity of results, abandon the study, and wait for others to take up the burden and begin all over again.

Any comprehensive estimate of the scope of the problems of lymphosarcoma must lead to the conclusion that unless there is a systematic attack over a long period by a group of competent workers, under favorable conditions, with adequate material support, and including all phases of the subject, it is unreasonable to hope for any great progress. With this conviction in mind, the writer ventures to outline a program of systematic investigation which might be expected to bring some light on the fundamental questions involved, and possibly lead to some progress toward the prevention and control of this group of diseases. In offering the plan, it is realized that syndicated research has seldom been very successful in solving the major problems of medicine and that there are many practical difficulties in carrying out any such prolonged program even under the best auspices.

#### PLAN OF SYSTEMATIC INVESTIGATION OF LYMPHOSARCOMA

*Clinical medicine* The clinician may investigate the importance of heredity, the relation to status lymphaticus, and the possible relation of the endocrine organs. Metabolic studies are indicated as affecting the soil for bacterial growth. The history of the main organ affected should be searched for. The usual clinical data should be analyzed statistically.

The epidemiology of the disease should be considered

*Pathological anatomy* Full autopsies and study of all organs should be obtained. Chronic lesions in the affected organs should be noted, especially the oropharynx and gastrointestinal tract. The pathology of metastases should be more carefully investigated and interpreted. Radiographs of injected tissues might give important data. The relation between structure and prognosis should be determined in a large series.

*Bacteriology* Bacterial studies of surgical and postmortem material should be pursued by appropriate methods. Little is known about the serology or immunology of the disease. The relation to bacterial antigens, and the effects of antigens made against whole tissues and tissue extracts and isolated bacteria invites attention. Bacterial mutation in the presence of lymphatic tissue is to be considered.

*Experimental pathology* The reactions of lymphatic tissue to all the common pyogenic bacteria, infectious granulomas, and many chemical agents should be systematically determined. The reactions of lymph nodes to various tissue extracts, lipoids, and proteins of the tumors should be studied. The element of hypersensitization of lymphatic tissue may be considered. The action of known cancerigenic chemicals should be determined in lymph nodes. Do specific agents act selectively upon lymphocytes and reticulum cells?

*Therapeutics* Radiological treatment should be standardized, and new modalities should be employed. The use of arsenicals in various combinations and as adjuvants to radiation is suggested by the work of Dustin. Antibacterial agents should be sought to control complications and terminal infections. The position of surgery should be determined.

*Diagnosis* The standard of general diagnosis should be improved by the collection of a large series of fully observed cases as in the Lymphatic Tumor Registry. There might well be established a central bureau where very experienced observers would furnish diagnosis and prognosis. The general literature of the entire subject should be made available.

Such a project should be located in an institution or center where material is abundant, and where all the necessary scientific and clinical aids would be available or constantly occupied with one or more of the main problems. If such an organization were established it would at least provide a center of reliable information and guidance which is now lacking, and it would soon reveal the futility of the present efforts directed toward the solution of one of the major problems of medicine.

## PRESENT STATUS OF SERUM THERAPY IN PNEUMONIA \*

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IT is interesting to compare the development of serum therapy for pneumonia with that of some other forms of specific therapy, such as diphtheria antitoxin for the treatment of diphtheria or insulin for the control of diabetes. In the two latter conditions the specific agents were produced in almost perfect form from the very beginning. Because of this perfection, the medical profession took hold of the new agents with much alacrity and enthusiasm and within a year after their introduction, diphtheria antitoxin and insulin were being widely used by physicians.

The serum therapy of pneumonia, on the other hand, has had a gradual evolution. There have been many obstacles to be overcome and considerable skepticism and indifference on the part of the medical profession to be combatted. The original Type I serum as produced by Cole<sup>1</sup> and his associates was applicable for only Type I pneumonia and, furthermore, the patient's sputum had to be typed by a laborious and time-consuming method before the serum could be administered.

The original Type I serum was bulky and had to be given in large quantities to be effective. As a result, inadequate amounts were often administered, and disappointing results were obtained. The large amount of horse protein in the serum caused severe serum sickness in many patients and the danger of anaphylactic shock and thermal reactions enhanced the unpopularity of the product. In spite of these drawbacks, however, the original Type I serum of Cole was an effective therapeutic agent. Its value was proven by the clinical and statistical evidence submitted by Cole and his co-workers,<sup>1</sup> and by the experimental studies of Cecil and Blake<sup>2</sup> on monkeys.

It has been just twenty-five years since the publication of the first articles on the use of Type I serum at the Hospital of the Rockefeller

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Institute<sup>1</sup> It is therefore a fitting time to review briefly the advances which have been made in the serum therapy of pneumonia during the last quarter of a century

First came the studies of Gay and Chickering,<sup>3</sup> Huntoon,<sup>4</sup> and finally the important investigations of Felton,<sup>5</sup> all of which showed that the specific antibodies in antipneumococcus serum could be separated by various chemical or biological procedures from the greater part of the protein content of the original serum Felton<sup>6</sup> went still further and succeeded in concentrating antibodies until the refined and concentrated product contained five or ten times as much antibody per unit of volume as the original serum The achievements of Felton simplified greatly the administration of serum and reduced considerably the incidence and severity of reactions

This improvement in antipneumococcus serum was followed by extensive statistical studies by Cecil and his co-workers<sup>7</sup> at Bellevue Hospital, by Bullowa<sup>8</sup> at Harlem Hospital, and by Heffron,<sup>9</sup> and Sutcliff and Finland<sup>10</sup> at the Boston City Hospital The results obtained in these studies in city hospitals were not only impressive clinically but afforded convincing statistical evidence of the value of pneumococcus serum in Type I pneumonia By using the alternate case method, it was shown that the death rate could be cut more than half by the use of serum When only early cases were included, the fatality rate was reduced from the standard 30 per cent to less than 10 per cent

The next important step in the development of antipneumococcus serum was the complete classification of pneumococci by Georgia Cooper and her co-workers<sup>11</sup> A Type II antipneumococcus serum had already been tried with promising results, but with the demonstration of thirty odd types of pneumococci, the whole field of serum therapy in pneumonia was greatly widened

It was fortunate that about this time Neufeld's<sup>12</sup> Quellung reaction was rediscovered and this led to a greatly simplified and accelerated method of typing pneumococci from the sputum and other body fluids Whereas heretofore it had been necessary to inject a mouse with the sputum and then wait eight to twenty-four hours before testing the exudate, it was now possible by the Neufeld method to determine the type directly from fresh sputum within an hour or two after the sputum had been sent to the laboratory This contribution has had a most important influence on the serum therapy of pneumonia, for even with



thirty odd specific antisera ready for administration to the pneumonia patient, much valuable time would be lost if we still had to determine the type by putting every sputum through the peritoneum of a white mouse

One of the most recent advances in the specific therapy of pneumonia has been the introduction of antipneumococcal rabbit serum. This work also emanates from the Rockefeller Institute, and the first report in 1937 by Horsfall, Goodner and MacLeod,<sup>13</sup> created wide attention and interest.

At the present time both horse serum and rabbit serum are available for the treatment of pneumonia. It will probably take several years of comparative study and investigation before we can be sure which serum has the greater merit. Some workers believe that rabbit serum is distinctly preferable to horse serum, others believe that so long as the serum is highly potent, it makes little difference from what animal it is derived.

No serum should be used unless its potency is known. The strength of serum is measured in units "per cc.," the unit being that amount of antibody which will protect a white mouse against one million fatal doses of virulent homologous pneumococcus culture.

Antipneumococcus serum is usually dispensed in vials containing ten to twenty thousand units. Cloudy serum should not be used. At the present time in the City of New York, the Department of Health provides antipneumococcal horse serum for Types I, II, V, VII and VIII. Some of the biological manufacturers, however, are going further, and provide antipneumococcal rabbit serum for the less prevalent types, such as Types III, IV, VI, XIII, XIV, XVII and XIX.

I believe that every case of pneumonia from which a definite pneumococcus type is determined and for which there is an available serum, should have serum therapy. Even apparently mild infections should usually receive serum, not only because it shortens the disease, but because an apparently mild pneumonia may suddenly become a very severe pneumonia. The only contraindications to serum therapy are terminal pneumonias and marked allergic states. With two types of serum available, it will often be possible to circumvent an allergic condition by giving a serum to which the patient is not sensitive. In patients with very low blood pressure, intravenous injections of glucose and saline may be given before starting the serum. In any case, the physician should have a good reason for withholding serum, for he assumes considerable re-

sponsibility in so doing

The use of antipneumococcal serum in the pneumonias of infants and children appears to be justifiable in many cases. I have had comparatively little experience with infantile pneumonia. However, C. H. Smith<sup>14</sup> at Bellevue Hospital and Bullock<sup>8</sup> at Harlem Hospital have both reported excellent results with serum therapy in the types of pneumonia which are most frequently encountered in childhood, namely Types I, VI, XIV and XIX. In children the serum may be given intramuscularly or intravenously.

### TESTS FOR SENSITIVITY

No patient should be given antipneumococcus serum without careful inquiry as to the incidence of hay fever, asthma and urticaria. Patients should also be questioned concerning previous injections of serum. Asthma is not necessarily a contraindication to serum therapy, provided there is no sensitivity to the serum that is to be employed, but in administering serum to an asthmatic, the physician should proceed with great caution.

*Intradermal Test* Once a decision has been reached to administer serum, the preliminary intradermal and conjunctival tests should be performed. For the intradermal test, two injections are made on the forearm at least two inches apart. The first contains a drop of 1:10 dilution of normal horse serum. The other, a small drop of physiological salt solution, serves as a control. In a positive reaction the wheal becomes larger and is surrounded by a zone of erythema. In a strongly positive reaction, pseudopodia are present. The conjunctival test is performed by inserting a drop or two of 1:10 dilution of normal horse serum in the conjunctival sac of one eye. In case of a positive reaction, the conjunctiva becomes injected and there is itching and watering of the eye. The readings for both tests should not be made for fifteen minutes after the injection of the serum. Antipneumococcus serum may be administered with caution in the presence of a weakly positive skin test. In the presence of a positive eye test, serum should be withheld.

*Desensitization* In a highly sensitive patient, desensitization is almost impossible to achieve and should not be attempted without consultation. The writer can recall two cases in which it was tried with very nearly disastrous results. A temporarily refractory state may be produced by means of adrenalin during which adequate doses of serum may often

be given. An injection of 0.5 to 1.0 cc of adrenalin five to ten minutes before the serum is administered usually suffices. Small doses of well-diluted serum are given first in gradually increasing amounts before attempting the full therapeutic dose.

Occasionally during the administration of serum, a crop of urticarial wheals appear, with intense itching. In such a case, the serum should be promptly discontinued and adrenalin given subcutaneously. After a short while, the remaining dose of serum may be administered.

A somewhat different procedure has been recommended before administering rabbit serum. A preliminary intravenous test is made by injecting 0.1 cc of the type-specific rabbit serum, diluted with 0.9 cc of saline solution. The pulse and blood-pressure are taken before the injection and five minutes following it. It is claimed that if a patient is sensitive to rabbit serum, there will be a fall in the arterial blood-pressure of twenty or more mm of mercury and an increase in the pulse rate of twenty or more beats per minute. In the presence of such a reaction, rabbit serum should not be administered.

#### ADMINISTRATION OF SERUM

If the sensitivity tests are negative, we proceed at once to the administration of serum. A syringe containing 1.0 cc of adrenalin should first be prepared to meet any emergency that might develop during the injection of the serum.

It is customary to give a small intravenous injection of serum before giving the full therapeutic dose. The amount injected differs in different clinics, usually 1.0 cc of serum, diluted with 9.0 cc of saline is administered very slowly with constant attention to the color and pulse rate of the patient. Such a small dose of course has no therapeutic value but if the patient takes it without any reaction, the physician will have a good deal more confidence in giving the full dose. If after one hour there is no reaction to the preliminary injection, we proceed to give 10 to 20 cc of serum intravenously depending on the potency of the agent. With the present concentration of serum it is possible to give the average complete dose of one hundred thousand units in three to four injections of serum. In bacteriemic cases, two hundred thousand units should be administered during the first twelve hours of treatment. On the morning after the injection of serum, patients who have been treated early usually show a striking improvement. The temperature and pulse rate will have

dropped to normal or almost normal and the whole appearance of the patient will have changed for the better. In cases in which marked improvement has not taken place within twenty-four hours after the injection of serum, the question will naturally be raised as to the accuracy of the typing. Unfortunately errors in typing are fairly common, though it must be added in defense of the bacteriologist that these mistakes often occur through no fault of technique. The first specimen of sputum may not contain the infecting type of pneumococcus at all, or it may yield two types of pneumococci, thus leaving the physician somewhat confused as to which type of serum to administer. Even in some correctly typed cases, however, little if any improvement will be noticed on the second day and it may be necessary to give more serum. This is particularly true in patients over forty-five years of age and in those with more than one lobe affected. It is also observed in cases where serum is started after the third day. In any case, serum should be continued until the temperature and pulse rate return to normal or until the intradermal or agglutination tests are definitely positive. The intradermal test and the agglutination tests are somewhat difficult to carry out unless the patient is in a hospital, and in the last analysis, neither is so dependable as the clinical condition of the patient.

An excellent rule to follow is to take a blood culture on every patient with pneumonia just before the administration of serum. The presence or absence of bacteriemia is of the greatest import so far as prognosis is concerned, and furthermore the dosage of serum is doubled in the presence of sepsis.

It is well to remember that when a lapse of several days has occurred since the administration of serum, the greatest caution must be observed if serum therapy is to be renewed. Otherwise a fatal anaphylaxis may occur.

In some clinics there is a tendency now to give the entire therapeutic dose of serum in one injection. This procedure has come into vogue since the introduction of rabbit serum. However, for the general practitioner particularly in treating a patient in the home it is a safer practice to divide the serum into several doses. There is also a tendency to give a larger dosage when using rabbit serum. Horsfall and his colleagues<sup>13</sup> at the Rockefeller Institute often give 250 thousand units of antibody with one injection of serum.

## SERUM REACTIONS

The various reactions to serum therapy are now familiar to most physicians. In the acute allergic reactions which appear during or shortly after administration, the patient becomes dyspneic, flushed and cyanotic, the pulse is rapid and weak and there is apprehension, tightness in the chest, and often a desire to urinate or defecate, in some cases there is also nausea and vomiting. In the occasional fatal reactions, the pulse becomes imperceptible and there is marked cyanosis followed by respiratory failure and death. Acute allergic reactions are promptly relieved by injections of 0.5 to 1.0 cc of adrenalin administered subcutaneously and well rubbed in. It is not necessary to inject the adrenalin directly into the vein. Thermal reactions are not so common now as they were in the early days of serum therapy. Occasionally, however, the patient will have a chill an hour or so after the injection of the serum, followed by a rise of one to four degrees in temperature. Usually there is a rapid drop, followed by profuse perspiration, but occasionally the temperature remains high ( $107^{\circ}$  to  $108^{\circ}$  F) and the patient may go into a profound shock and stupor. In case of hyperpyrexia, cold packs and ice water enemas should be used together with emergency stimulation. Serum sickness is another form of serum reaction which is much less frequently seen now than formerly. The giant urticaria which so often followed serum in the early days is now a rare complication. Mild urticaria develops in 15 to 20 per cent of patients who receive the modern concentrated and refined forms of antipneumococcus serum.

## RESULTS OF TREATMENT

The introduction of antipneumococcus serum has revolutionized the treatment of pneumonia. The use of serum not only reduces the fatality rate by more than one-half but, if given early, prevents bacteremia and greatly shortens the duration of the disease. The results of serum therapy for the various types are shown in Table I.

These figures have been compiled from the statistics of a number of different observers. The largest series is naturally the Type I group, for which serum has been used for many years. The death rate is cut from 32.6 per cent for controls to 13.6 per cent for serum treated cases. The results of serum treatment in Type I pneumonia have been remarkably consistent. For example, Lord and Heffron<sup>16</sup> report 1043 cases of

TABLE I

FATALITY RATES FOR PNEUMOCOCCUS PNEUMONIA OF  
THE COMMONER TYPES, WITH AND WITHOUT SERUM\*  
(HORSE SERUM ONLY)

<i>Type of Pneumococcus</i>	<i>Serum Treated</i>			<i>No Serum</i>		
	<i>No of Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>	<i>No of Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>
I	3136	429	13.6	558	182	32.6
II	964	302	31.3	967	424	43.8
V	139	35	25.1	516	187	36.2
VII	109	13	11.9	404	117	28.9
VIII	41	4	9.8	319	60	18.8
XIV	39	4	10.2	167	34	20.3
TOTAL	4428	787	17.7	2931	1004	34.2

TABLE II

FATALITY RATES FOR PNEUMOCOCCUS TYPES I & II  
TREATED WITHIN AND AFTER SEVENTY-TWO HOURS

<i>Pneumococcus</i>	<i>Cases Treated Within 72 hours of onset</i>			<i>Cases Treated 72 hours, or more, after onset</i>		
	<i>No Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>	<i>No Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>
Type I	844	79	9.3	979	170	17.3
II	62	10	16.1	40	16	40.0

TABLE III

## RESULTS OF SERUM THERAPY IN BACTERIEMIC CASES OF PNEUMONIA

<i>Pneumococcus</i>	<i>Serum Treated</i>			<i>No Serum</i>		
	<i>No Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>	<i>No Cases</i>	<i>Deaths</i>	<i>Mortality Per Cent</i>
Type I	651	225	34.5	325	225	69.6
II	189	105	55.5	381	282	74.0
V	36	26	72.2	113	87	76.9
VII	13	2	15.4	71	61	85.9
VIII	15	5	33.3	126	57	45.2
TOTAL	904	363	42.2	1016	712	70.0

\* The figures presented in Tables I, II and III have been compiled from the published statistics of various writers

Type I pneumonia treated with serum with a death-rate of 13.9 per cent. Rogers<sup>16</sup> reports that in 1023 cases of Type I pneumonia, treated with serum during the first four days of the disease, the death rate was also 13.9 per cent<sup>1</sup>. Even lower figures have been obtained by Cole<sup>17</sup> at the Rockefeller Institute and by Bullowa<sup>8</sup> at the Harlem Hospital. Cecil and Plummer<sup>7</sup> obtained a higher figure at Bellevue, where 410 Type I pneumonias that received specific therapy had a death rate of 17.6 per cent.

In Table I it will be noted that the fatality rates for the other prevalent types of pneumonia are also very favorably affected by serum therapy. The total for 4428 cases of pneumococcal pneumonia treated with specific serum yields a fatality rate of 17.7 per cent, compared with 34.2 per cent for 2931 cases that received no serum.

Both Type II and Type III pneumonia have offered considerable resistance to serum therapy, presumably because they are both severe forms of pneumonia and have a natural fatality rate of 40 to 50 per cent. Thanks to more potent serum, Type II is now being favorably affected by specific therapy, but Type II pneumonia should be very promptly treated and with large doses of serum. In Table II we show the importance of administering serum early in the disease.

The fatality rates of serum-treated cases are distinctly lower for those patients treated within the first seventy-two hours than for patients treated seventy-two hours, or more, after the onset of the disease.

In bacteriemic cases, the death rates for all types of pneumococcal pneumonia are double or triple the usual figure but here again the value of serum therapy is well shown. In Table III, the results of serum in bacteriemic cases are shown for the five prevalent types.

The fatality rate for septic cases treated with serum is 42.2 per cent, compared with 70 per cent for the septic cases that received no serum.

*Type III Pneumonia* Pneumococcus Type III pneumonia still presents a serious therapeutic problem and because of the disappointing results obtained with serum therapy, efforts have been made to control the disease by chemotherapy, or by a combination of serum therapy with chemotherapy. For example, Rosenthal,<sup>18</sup> Long and Bliss,<sup>19</sup> and Cooper, Gross and Mellon<sup>20</sup> have reported favorable results with sulfanilamide in white mice and rats infected with pneumococcus Type III.

Heintzelman<sup>21</sup> has recently reported a series of nine cases of pneumococcus Type III pneumonia treated with sulfanilamide, with a fatality rate of only 22 per cent. The series is too small, however, to be of

much significance. In the very interesting bone marrow studies of Osgood,<sup>22</sup> the author showed that Type I antipneumococcal serum was more effective against Type I pneumococcus than sulfanilamide. However, he then showed that sulfanilamide plus a given dose of antiserum was more effective than corresponding doses of antiserum alone. His results support the view that sulfanilamide renders the pneumococcus more vulnerable to bactericidal substances present in the serum. In view of these findings, it would seem that further observations on the combined effect of sulfanilamide and type-specific antipneumococcal serum are in order.

Because of the favorable results obtained with sulfanilamide in frank *Streptococcus hemolyticus* infections, it is natural that chemists should be striving to obtain some derivative of sulfanilamide which will exercise a similar specific effect on pneumococcal infections. Up to date, the most promising synthetic agent of this kind is that advocated by Whitby,<sup>23</sup> who observed that 2-(p-aminobenzene-sulphonamido) pyridine protects mice effectively against 10,000 lethal doses of Types I, VII and VIII. This drug is frequently referred to as Dagenan or M & B 693. Fleming,<sup>24</sup> working with the drug *in vitro*, noted that its effect was bacteriostatic rather than bactericidal. He found no deleterious effect from the drug on the leukocytes and further noted that the efficiency of the agent was enhanced in the presence of specific immune serum. He suggested that to obtain the best results, the patient should be given specific serum as well as M & B 693. The drug appears to be less toxic than sulfanilamide though, if kept up for any time, it frequently causes nausea and vomiting. Evans and Gaisford<sup>25</sup> have recently reported in the *Lancet*, 100 cases of pneumococcus pneumonia treated with M & B 693. A control series of 100 cases was observed at the same time. A fatality rate of only 8 per cent was observed in the treated cases while that for the untreated cases was 27 per cent. The weakness in this report is that quite a large proportion of the cases treated were not typed. At the present time Dagenan (M-B 693) is being tried out clinically in a number of New York hospitals. In many cases the results have been quite striking but in certain other cases, especially those treated late, the drug has not prevented a fatal termination. Perhaps the ideal combination may eventually prove to be a combination of specific serum with chemotherapy. Under any circumstances Dagenan must be looked upon as an important and promising addition to our pneumonia therapy, though



obviously still in the experimental stage

The writer wishes to say a final word about the treatment of pneumonia in private practice. In a recent study with E. A. Lawrence,<sup>26</sup> we analyzed 911 cases of pneumonia from the records of private practice with especial reference to the incidence and fatality rates for different types and the results of serum therapy. The data obtained from the private practice series were compared with well-established data based on records from the public wards of large city hospitals. The most significant facts brought out by this study were

- 1 The generally higher age incidence of pneumonia in the well-to-do classes

- 2 The high incidence of pneumococcus Type III pneumonia in private practice. This probably resulted from the higher age incidence of this group

- 3 Inadequate bacteriological study of private cases. Less than half of the patients available for the study had been properly typed

- 4 Only 60 per cent of the private pavilion patients with Type I pneumonia received Type I serum. In the consultation series, a higher proportion received serum but the results of serum therapy in both series were not so favorable as those obtained in the wards of large city hospitals. The fatality rate of 23.5 per cent for the entire series of 115 private cases of Type I pneumonia in which serum therapy was given is almost double that reported from various other sources and is not conspicuously lower than the standard fatality rate for Type I non-serum treated cases. A number of factors such as the higher age incidence, delay in administering serum, and inadequate dosage of serum are presumably responsible for this high figure. Pneumonia in private practice is not so mild as it has often been considered. In view of the proven value of serum therapy in pneumonia, the administration of serum should be part of the routine treatment in every case amenable to serum therapy, regardless of the social status of the patient.

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## TREATMENT OF PNEUMONIA WITH ANTIPNEUMOCOCCAL RABBIT SERUM\*

COLIN M. MACLEOD

**S**TUDIES of the differences in the physical, chemical, and immunological properties of horse and rabbit antipneumococcal serum led to the conclusion that rabbit serum might have certain advantages over horse serum as a therapeutic agent in pneumococcal pneumonia

Certain of these differences have been known for a number of years. In 1923 Zinsser and Parker<sup>1</sup> observed that *in vitro* complement fixation does not occur when the specific pneumococcal polysaccharides are mixed with immune horse serum, whereas it does take place in mixtures of these polysaccharides and immune rabbit serum.

Avery and Tillett<sup>2</sup> demonstrated that the injection of horse antipneumococcal serum does not passively sensitize guinea pigs to subsequent injection of the specific pneumococcal polysaccharides, while with immune rabbit serum the guinea pig can be passively sensitized.

Similarly, it was found by Heidelberger and Goebel<sup>3</sup> that horse and rabbit antipneumococcal serum differ in their precipitin reactions when mixed with the partially hydrolyzed specific polysaccharide. This was further investigated by Heidelberger and Kendall<sup>4</sup>.

Goodner<sup>5</sup> noted that rabbit antipneumococcal serum was more effective than horse antiserum in the treatment of rabbits infected by the intradermal injection of virulent pneumococci.

The introduction in 1929 of the quantitative precipitin method by Heidelberger and Kendall<sup>6</sup> opened the way to the more exact study of the immunological behavior of antipneumococcal sera. It was shown by Heidelberger, Sia, and Kendall<sup>7</sup> that the antibody content of horse antipneumococcal serum as measured by mouse protection tests, paralleled fairly closely the amount of specifically precipitable nitrogen in such serum. This was also found to be true of rabbit serum by Heidelberger and Kendall<sup>8</sup>.

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By comparing the amount of specifically precipitable nitrogen with the mouse protective potency of both horse and rabbit serum, Goodner and Horsfall<sup>9</sup> demonstrated that each milligram of specifically precipitable nitrogen in rabbit serum corresponds to approximately 1200 mouse protective units, whereas with horse serum the same amount of specifically precipitable nitrogen represents between 500 and 800 mouse protective units. The use of the quantitative precipitation method, and the extension of this principle by Heidelberger and Kabat<sup>10</sup> to the quantitative determination of agglutinin nitrogen has been of great value in the standardization of rabbit antipneumococcal serum and will be discussed briefly later.

Goodner, Horsfall and Bauer,<sup>11</sup> by the technique of ultrafiltration through graded collodion membranes, determined that the antibody protein molecule of immune rabbit serum is much smaller in size than that of horse serum. Heidelberger, Pedersen and Tiselius<sup>12</sup> reached the same conclusion using the technique of ultracentrifugation. These observations explain in part the difference in the amount of protein nitrogen precipitated from immune horse and rabbit serum by the specific pneumococcal polysaccharides.

In experimental pneumococcal infections in the mouse the amount of immune horse serum which must be used to overcome the infection has been found to lie within certain limits. If an excess of horse serum is given, the protective action may disappear entirely. This "prozone" phenomenon was not observed by Goodner and Horsfall<sup>13</sup> in the case of immune rabbit serum.

In mouse protection experiments, the same investigators<sup>14</sup> noted that small amounts of cholesterol or cephalin block the protective action of horse antipneumococcal serum but are without effect in the case of rabbit serum. Although the significance of these observations as applied to pneumococcal infections in man is unknown, they are nevertheless of great theoretical interest.

Certain practical considerations were emphasized by Horsfall, Goodner and MacLeod<sup>15</sup> in suggesting the use of rabbit antipneumococcal serum in the treatment of pneumonia. Up to the present time it has been relatively difficult to produce in the horse serum of high titer against pneumococci of certain types. This has been particularly true of Type II serum. On the other hand in the rabbit provided certain precautions are observed in the preparation of the suspensions of pneumococci to be

used for immunization,<sup>16</sup> serum of high potency can be prepared against pneumococci of practically all types. Even in the case of Type III pneumococcus, antiserum of moderately high titer has been obtained fairly regularly in the rabbit, whereas serum of high titer can be produced in the horse only irregularly and with great difficulty. The relative ease of immunizing rabbits with pneumococci of the various types has been one of the strongest arguments in favor of using this serum and has led to its present widespread employment against pneumococcal infections of many types. It is of interest that in the rabbit within a period of from four to six weeks, Type I antipneumococcal serum can be prepared, which in its unconcentrated form has frequently the same potency as the concentrated Type I horse serum in current use.

The standardization of antipneumococcal serum has always presented certain difficulties. The method currently used is that of mouse protection employing a standard serum as a reference. In this technique, unless very large numbers of mice are used, the accurate standardization of serum is impossible. The estimation of the amount of specifically precipitable nitrogen in rabbit serum, however, provides a more precise method, since the ratio between specifically precipitable nitrogen and mouse protective units is practically constant in rabbit serum under given experimental conditions. This method has not been applicable to the standardization of horse serum, since it appears to contain antibody fractions of differing avidity for the specific pneumococcal polysaccharide, and these fractions show wide differences in their mouse protective capacity.<sup>9</sup> Consideration of these and other differences in the behavior of horse and rabbit antipneumococcal serum led to the clinical trial of rabbit serum in the treatment of pneumonia.

The same procedures which have been widely employed for the testing of patients for sensitivity to horse serum are applicable to sensitivity tests with rabbit serum as well. Most important of all is an accurate history with reference to allergy, and previous parenteral administration of foreign protein.

Individuals who have acquired sensitivity as a result of previous injections of horse serum, are not ordinarily sensitive to rabbit serum. However, it must be borne in mind that patients with a history of allergy, for example, those who suffer from allergic asthma and are known to be sensitive to horse serum, are also likely to be sensitive to rabbit serum.

In order to determine sensitivity to rabbit serum, intradermal and intraconjunctival tests are made with normal rabbit serum diluted 1:100 with salt solution, precisely as with horse serum. The dilution of 1:100 is important, since when normal rabbit serum is used intradermally in a dilution of 1:10, the skin of many patients will show a non-specific flare reaction. This may be difficult to distinguish from the true allergic reaction which consists of a wheal with surrounding erythema.

The intravenous injection of a small amount of serum is not to be recommended without first knowing the results of the skin and eye tests, since anaphylactic shock may occasionally occur in extremely hypersensitive individuals following the intravenous injection of as little as 0.1 cc of well diluted serum. As a further precaution after the results of the skin and eye tests are known, it has been our practice to inject slowly intravenously 0.1 cc of the therapeutic serum diluted to 50 cc with normal saline. If a fall in blood pressure and an elevation of the pulse rate do not occur, it is considered safe to proceed with the therapeutic dose of serum.

The reactions which may occur following the intravenous injection of therapeutic amounts of rabbit serum correspond to those following the use of horse serum. These are (a) anaphylactic shock, (b) the accelerated or anaphylactoid reaction, (c) the chill reaction, (d) serum sickness. Only the last two of these reactions will be discussed at this time.

*Chill reaction.* Considerable work has been done on the factor or factors in salt solution and solutions of foreign protein which cause chill reactions. There is no unanimity of opinion as to whether the chill-producing substances are extrinsic or intrinsic in origin. Although methods employed for removing these substances either by processing or by fractionation and concentration of the serum have not been uniformly successful, progress in this direction has been made.

Not every lot of unconcentrated rabbit serum produces chills. Indeed, in certain cases amounts as great as 200 cc or even 500 cc may be injected intravenously in a single dose without producing any thermal reaction whatever. Similarly, the amount of chill-producing substances varies greatly from one lot of rabbit serum to another. Certain lots contain only a small amount, so that 50 cc or more of serum can be injected intravenously without the occurrence of a chill, whereas the injection of 100 cc of the same serum may produce a thermal reaction.

If at the time of injection of the larger amount of such relatively non-toxic sera, 0.6 to 0.9 gm of acetylsalicylic acid is given by mouth, the chill reaction may be entirely prevented. However, this drug is not effective when serum is used containing a higher concentration of the chill-producing factor.

In a search for substances which might relieve the chill reaction, Beeson and Hoagland<sup>17</sup> observed that in about 50 per cent of cases the intravenous administration of calcium chloride would abort almost instantaneously the chills following the injection of rabbit serum. However, this agent is effective in relieving only the milder chill reactions.

*Serum sickness* Serum sickness following the administration of rabbit serum has occurred in 65 per cent of cases. This is almost the same incidence of serum sickness as that which we have observed following the use of concentrated horse antipneumococcal serum. The manifestations of serum sickness do not differ from those seen when horse serum is employed.

The use of unconcentrated rabbit antipneumococcal serum in the treatment of pneumonia due to pneumococci of various types has been previously described in two reports from this hospital.<sup>18</sup> In the second paper a number of patients were included who had been treated in other institutions with the same lots of serum. The present report deals only with patients who have been treated in the Hospital of the Rockefeller Institute.

In Table I are shown the results which have been obtained in the treatment of pneumonia in this hospital using unconcentrated rabbit serum.

A total of 100 patients, including infections due to pneumococci of nine different types, has been treated. Eleven patients have died—a mortality of 11 per cent. Of the eleven who died, seven suffered from Type III pneumonia. The final judgment on the efficacy of Type III rabbit antipneumococcal serum has not been made, but in a certain group of patients a beneficial effect has occurred, particularly in individuals before the sixth decade. In such patients a dramatic response may occur, similar to that which is seen so frequently in the serum treatment of Type I pneumonia. Of the patients with Type III pneumonia who died, only three could be considered as having received adequate dosage of serum by our present standards, but the fact that these patients died despite intensive treatment makes it imperative to pursue further the investiga-

TABLE I  
MORTALITY RATE IN 100 PATIENTS TREATED WITH  
UNCONCENTRATED RABBIT ANTIPNEUMOCOCCAL SERUM

<i>Type</i>	<i>Number of cases</i>	<i>Number of deaths</i>
I	28	1
II	10	2
III	26	7
IV	4	1
V	3	—
VI	2	—
VII	10	—
VIII	9	—
IX	4	—
XIV	2	—
XVIII	1	—
XIX	1	—
Total	100	11 (11%)
Excluding Type III cases	74	4 (5.4%)

tion of the therapy of Type III infections

Because of the questionable efficacy of Type III serum it seems fair to exclude the twenty-six cases of Type III pneumonia from the series. If this is done, the mortality rate is only 5.4 per cent—four deaths in seventy-four cases of pneumonia. The patients who died, other than those in the Type III group, illustrate what has long been known concerning antipneumococcal serum therapy in general, namely the advantage of early treatment. All but one of these patients were treated late in the disease, in two, empyema was present associated with severe bacteremia, one patient had meningitis at the time of admission, and the fourth patient was an elderly man with Type II pneumonia, who had consolidation of four pulmonary lobes when admitted to hospital.

A similar experience with rabbit antipneumococcal serum is reported by Loughlin and his co-workers from the Long Island College Hospital.<sup>19</sup> Sixty-nine patients with pneumonia due to Types I, II, V, VII, VIII and XIV were treated, with a mortality rate of 7.4 per cent.

During the past two years an attempt has been made in each case to administer the required amount of antibody within as short a period as possible. Great assistance has been rendered in this study by using the skin test with the specific polysaccharide of the homologous type as an aid in the control of dosage. Francis<sup>20</sup> showed that when a patient had received an amount of Type I serum sufficient to initiate recovery the intradermal injection of Type I polysaccharide would result in a wheal



TABLE II  
DEFERVESCENT TIME IN TYPE I CASES TREATED  
WITH HORSE OR RABBIT SERUM

<i>Antipneumococcus serum used</i>	<i>Method of administration</i>	<i>Number of cases</i>	<i>Defervescence— average time in hours</i>
Concentrated horse serum	Divided doses	25	22.6
Unconcentrated rabbit serum	Single and divided doses (all cases)	26	13.8
Unconcentrated rabbit serum	Within two hours	16	9.3

TABLE III  
DEFERVESCENT TIME IN CASES TREATED  
WITHIN EIGHT HOUR PERIOD

<i>Type</i>	<i>Number of cases</i>	<i>Defervescence— Average time in hours</i>
I	19	11.1
II	4	6.7
III	5	11.2
IV	3	8.0
V	3	7.3
VI	1	6.0
VII	5	8.6
VIII	5	9.8
IX	2	11.5
XVIII	1	7.0
Total	48	9.75

and erythema reaction at the site of injection. This test has proved a valuable guide to serum dosage with horse and rabbit serum of several types, since on the development of a positive skin test, serum therapy may be safely discontinued.<sup>21</sup>

Table II shows the average time required for defervescence in patients with Type I pneumonia treated with concentrated horse serum, and in patients receiving unconcentrated rabbit serum. With concentrated horse serum, treatment was carried out by the divided dose method, serum being given at two to four hour intervals. Defervescence in these twenty-five cases occurred in an average of 22.6 hours from the beginning of treatment. In twenty-six cases treated with unconcentrated rabbit serum, defervescence occurred in an average of 13.8 hours. However, of these twenty-six cases, sixteen received the full therapeutic amount of serum in less than two hours, and in this group defervescence occurred on the average in 9.3 hours.

The same method of intensive therapy has been applied to the treatment of pneumonia due to other types as well. Table III shows the results obtained in forty-eight cases. In many instances the full therapeutic dose of serum was given at one injection shortly after the patient was admitted to hospital. In the remainder, treatment was completed within eight hours. The average time required for defervescence was only 9.75 hours. In practically all of these cases the skin test with the specific polysaccharide was employed to determine when sufficient serum had been given.

The effective amount of rabbit antipneumococcal serum varied from case to case, and at present no definite rules regarding dosage can be stated. We feel that in the adult patient with uncomplicated Type I pneumonia of not more than three days' duration, a dose of 125,000 units should be given as soon as possible. After the third day a somewhat larger initial dose should be given, particularly if the consolidation involves more than one pulmonary lobe, or complications such as bacteremia are known to be present.

The favorable results which have been obtained in this relatively small series of cases have probably been due in part to the administration of a highly potent serum and in part to intensive treatment controlled by an accurate method for determining the required dosage.

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#### DEATHS OF FELLOWS

DOUGLAS, JOHN 568 Park Avenue, New York City, born in New York City August 5, 1875, died in New York City December 5, 1938, received the degree of Bachelor of Science from the College of the City of New York in 1894 and graduated in medicine from the College of Physicians and Surgeons, New York, in 1898, elected a Fellow of the Academy January 5, 1905 and served as Chairman of the Section of Surgery, 1915-16

Dr Douglas had been attending surgeon to the St Luke's Hospital since 1927 and president of its medical board 1932-33 consulting surgeon to the Bellevue Hospital since 1927 consulting surgeon to the Harlem Y and Bar Hospital since 1929 and consulting surgeon to the Knickerbocker Hospi-

tal since 1930 He was an instructor at New York University and Bellevue Medical College, 1904-12, and clinical professor of surgery at New York University since 1912

Dr Douglas held a certificate from the American Board of Surgery, and was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the American Surgical Association, the New York Surgical Society and its president, 1931-32 the County Medical Society and its president in 1928, and the State Medical Society He was an alumnus of St. Luke's Hospital, Bellevue Hospital and Sloane Hospital for Women

Dr Douglas was the author of many articles and reports on surgical subjects

GOTTIHERF MARK JACOB 239 West 75 Street, New York City born in Montrose, Pennsylvania in 1887 died in New York City, December 21 1938 graduated in medicine from New York University and Bellevue Hospital Medical College in 1909 elected a Fellow of the Academy October 5, 1922

Dr Gottlieb was associate otolaryngologist to the Harlem Hospital. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American Medical Association and a member of the County and State Medical Societies.

HORN, WALTER LOUIS 1010 Park Avenue, New York City, born in New York City, March 1, 1891, died in New York City December 29, 1938, graduated in medicine from Fordham University Medical School in 1916, elected a Fellow of the Academy May 4, 1922.

Dr Horn was associate otologist to the Mount Sinai Hospital, assistant surgeon to the Manhattan Eye, Ear and Throat Hospital, surgeon director of otolaryngology to the Misericordia Hospital and assistant otorhinolaryngologist to the Metropolitan Hospital.

Dr Horn was a diplomate of the American Board of Otolaryngology, a fellow of the American College of Surgeons, the American Medical Association and a member of the American Academy of Ophthalmology and Otolaryngology, and the County and State Medical Societies.

LOPEZ, JOSE ANTONIO 220 West 98 Street, New York City, born in San Germán, Puerto Rico, May 8, 1881, died in New York City, November 19, 1938, graduated in medicine from Syracuse University Medical College in 1904, elected a Fellow of the Academy November 6, 1919.

SUTTON, LUCY DEBOIS PORTER 168 East 74 Street, New York City, born in Bridgewater, Massachusetts, February 16, 1891, died in New York City, December 23, 1938, graduated in medicine from Cornell University Medical College in 1919, elected a Fellow of the Academy January 6, 1927, elected Secretary of the Section of Pediatrics May 12, 1935.

Dr Sutton was assistant professor of pediatrics at Cornell University Medical College and associate visiting physician to the Children's Medical Service at Bellevue Hospital.

Dr Sutton held a certificate from the American Board of Pediatrics and was a member of the American Public Health Association and the American Academy of Pediatrics.

BULLETIN OF THE NEW YORK  
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BULLETIN OF  
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MARCH 1939

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ADDRESS OF THE RETIRING PRESIDENT\*

JAMES ALEXANDER MILLER

MY DUTIES and responsibilities upon this occasion are relatively unimportant and what I have to say will not detain us long from the main object of this annual meeting which is to usher in a new administration of the affairs of the Academy

A very brief summary of our activities during the past year is, however, in order, but the details are contained in the various reports which have been presented to you this evening by title and which will be published in full in the regular annual report of the Academy. I trust they will receive from the entire membership the careful attention which they deserve.

The Trustees under the able chairmanship of Dr. Niles have managed the business affairs of the Academy with great devotion and skill. Our financial resources have been conserved with considerable success in the face of the great difficulties imposed by the general economic uncertainty and particularly and due largely to the efficient management of our Comptroller, Mr. Eberle, the Trustees have been able to place our investments in real estate mortgages upon an extraordinarily sound basis.

The general financial situation of the Academy has been the subject of great concern and the most careful study during the entire year. The

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expanding activities and responsibilities of the Academy call for financial expenditures beyond our regular income. The Council and Trustees believe that these expenditures can not be materially curtailed without serious handicap to the program to which we are committed. It was determined therefore to make a systematic attempt to increase our income. Through a special committee, of which Dr. Krech is chairman, this effort has been very successful, but we still need additional funds, to obtain which the activities of this committee will be continued. I bespeak the even greater co-operation of the members of the Academy in order that this committee may attain the objects in mind.

Although it has been the opinion of the Council that all of the present activities of the Academy are important and essential, in view of the budgetary situation and also in accord with sound policy, the Council has authorized a very thorough-going study of all of the Academy activities. Through a large committee, divided into several subcommittees and under the general chairmanship of Dr. George Baehr, this analysis is now being made and its results will be available soon and will serve as an accurate basis upon which to formulate both the program and the budget for next year.

A quite unexpected and serious problem has recently been presented to the Trustees and Council by a request from the Federal Bureau of Internal Revenue to show cause why the Academy of Medicine should longer be exempt from taxation. At first it did not seem that this could be a serious request as the Academy ever since its original organization in 1847 has been exempt from all taxation as a quasi-public educational institution. This request soon developed, however, into a very serious and determined effort and it was only by the most detailed and skillful presentation of our case by our Director, Dr. Hartwell, and our legal counsel that our continued exemption from taxation was finally allowed. It is, however, important that all of our members should be made aware that the only basis for this favorable decision was the evidence presented of the large amount of education and of service that the Academy renders the community as a whole. It was the occasion for great gratification that a very large number of persons important in both public and private life in New York rallied to our support and offered the most enthusiastic testimony to the invaluable services that the Academy is rendering to the community. This incident should serve as a serious warning to future officers of the Academy and particularly to those members who have

entertained doubts concerning the wisdom of our policy to extend our services to the public as well as to our own membership

As to the regular activities of the Academy I will comment very briefly and only to state that the work of the Library, of our Medical Education, of our Public Health Relations, and of the Medical Information Bureau have, under the direction of our various committees continued to operate upon the high level of efficiency which we have become accustomed to expect

I may, however, take this occasion to emphasize the great success of the Committee on Education in the development of the Graduate Fort-night and the Friday Afternoon Lectures, and also I am personally particularly grateful for the inauguration of a new policy concerning the programs for the Stated Meetings Largely through the initiative of a subcommittee of which Dr Chace is chairman, these meetings have been transformed from a nightmare for the presiding officer to an occasion of great pleasure and educational profit Also, I desire to record my great satisfaction in the action taken by the Academy tonight in transferring the Medical Information Bureau to the status of a regular standing committee of the Academy This activity of the Academy is its most recent one and has furnished the occasion for deep searching of hearts on the part of the officers and some of our members The Council has now however, definitely taken the position that this service is not only a proper but also an important activity for the Academy to undertake and by so doing it has approved the judgment of our late Director, Dr Linsley Williams, through whose efforts this Bureau was originally established

To a considerable extent the work of this Bureau is still in a pioneer field and is too little known and appreciated by our membership as a whole Its function may be briefly though inadequately summarized to consist in providing a clearing house for medical information for both physicians and laymen and especially to interpret new steps in the progress of medical science and to guide the method of its communication to the public, especially through the public press and the radio In addition, the Bureau has organized a very successful annual series of Lectures to the Laity

This program presents many new and at times knotty problems and to meet them the Committee and its executive secretary are aided by a special staff of experts in every field of medicine selected from the membership of the Academy

By sanctioning this Bureau, the Academy has placed itself upon the side of general public education in medical matters and has discarded the theory that medical knowledge should be confined strictly to the medical profession. Mistakes and misinterpretation will inevitably occur in this field but it is not only my personal belief but also that of the Council that the program as a whole is most useful and is destined to be increasingly valuable by fostering better mutual understanding between physicians and the public which they serve. It is certainly in line with the spirit of the times and this was one of the public services of the Academy which favorably impressed the Bureau of Internal Revenue in its recent investigation of our activities. I hope that more of our members will get to know and understand this Bureau better.

While we are considering the relations of the Academy to the public, I would like briefly to touch upon another aspect of this question.

I have frequently been asked, "What is the position of the Academy of Medicine regarding the seething discussions which are going on concerning what is rather loosely termed, Socialized Medicine?"

As I understand it, it is the policy of the Academy not to participate actively in any discussion of the social and economic problems which concern primarily the organization of medical practice either in relation to society as a whole or to the State. This is the function of other duly authorized representatives of the medical profession.

As individuals, however, we are of course deeply concerned especially when the situation has developed that our profession is classed as a trades union and is indicted for maintaining a conspiracy in restraint of trade. We are indignant at the grossly unfair position into which these charges have forced us and we believe that this feeling is shared by most of the laity with whom we come in contact in our practice. As an Academy, however, we have no intention of jumping into the arena, but that a situation is developing which may have serious consequences, not only for the medical profession but also for the public which we serve, there can be no doubt.

It would seem to me that as an educational institution the Academy has an opportunity and a responsibility to be indirectly of great service in this matter. In the first place we know that really adequate medical service depends upon quality rather than quantity or methods of distribution. We know the rapid progress that has been and is being made both in medical knowledge and its practical application. We also know,

none better, that much inadequacy and imperfection as well as lack of knowledge still exist

It would appear to be the duty of medical educational institutions like the Academy to redouble their efforts to remedy defects when possible and to maintain even higher standards in practice and in ethics than have been achieved in the past. The Academy can do this.

In the second place we can extend our efforts to educate the public so that it may better understand, not only what we have done and are doing, but also what we have thus far failed to do and why. The public should know something of our difficulties and our problems as well as of our achievements, should appreciate the fact that real success in this difficult field cannot be obtained through legislation or State control, and finally should realize that our success or failure in overcoming our difficulties means even more to them than it does to us, and that to succeed we need their understanding as well as their help and co-operation.

In a democracy like ours the ultimate power is with the people and they, not the medical profession, will decide this question. From our vantage ground of more intimate knowledge we can but guide and help the people to reach a wise decision. Toward this end we should increase and extend rather than curtail our efforts to educate the public in medical matters. This also the Academy can do.

It would be impossible to relinquish the office of your President without expressing to you my deep appreciation of the services of the executive staff of the Academy and of the wonderful spirit which animates them throughout. It is they who make the Academy what it is and we as officers and members alike can never cease to be grateful to them and appreciative of their devotion.

Among such a fine group of people one hesitates to single out any one for especial mention. It, however, could surely not be considered invidious to point out that my executive staff takes its cue from its leader and in its leader, our Director, Dr. Hartwell, both the staff and the entire Academy have come to recognize a personality possessed of a rare combination of efficiency, good judgment, sympathetic understanding, political insight, and capacity for hard work. For five years the Academy has been his man, in fact it would seem as though it must have been his sole interest, so devoted has he constantly been to its welfare. That this has been so in spite of great physical handicaps and suffering makes his

achievement truly remarkable and stamps him as a man of the highest courage as well as of high ideals. The Academy during its memorable history has enjoyed the devoted services of many notable officers, but I venture to assert that none will ever be regarded as having been more notable or more devoted than John A. Hartwell.

This now brings me to a very unwelcome task. I have to announce that Dr. Hartwell has presented his resignation as Director and that the Council has accepted it to take effect April 1, 1939. He will not really leave us for his influence will long probably always be with us, but we are sad at his going and all of us, officers, staff and members alike, bid him God speed and wish him many more years of renewed health, of service, and of happiness.

It was more than a year ago that Dr. Hartwell presented his resignation to the Council to take effect at its pleasure. With the inevitable prospect ahead that his successor must ere long be found, a special committee was appointed to canvass the situation and make recommendations to the Council. This committee has worked very hard and most faithfully. Its first objective was to find a comparatively young man who possessed the necessary qualifications. In that they were unsuccessful. They then explored the possibilities of the older age groups. In that they have been eminently successful and some of us, perhaps because we too are older, were glad, because we visioned the Academy as in need of a leader of ripe experience and seasoned judgment in these perplexing times.

The committee recommended to the Council the name of a man who stands very high in our profession as a clinician and as a teacher, who has had the experience of directing the clinical and research activities of a great hospital, who has served actively for many years upon various important committees and more recently as a Vice President of the Academy. He has demonstrated outstanding ability and also possesses personal qualities which will make for understanding co-operation and inspiring leadership. By invitation of the Council, our Director after April first will be Dr. Herbert B. Wilcox.


And now my task and my responsibilities are at an end. It remains only first to express to all of you, officers, staff and members, my deep appreciation of the great privilege that has been mine to have served as your President during the past two years. These years have greatly deepened my appreciation of and affection for this great institution. I would that I might have been able to be more effective and if perchance

anything of value has been accomplished, it has been only because of your splendid and devoted support for which I will always be in your debt

And secondly and finally there remains to me a great pleasure and privilege, that is, to introduce to you your new President

I have known him intimately for nearly fifty years I have never known him to fail, either in friendship, in character or in devotion to the highest ideals of our profession You may be assured that he will not fail you

Your President' Dr Malcolm Goodridge





## PRESIDENTIAL ADDRESS\*

MALCOLM GOODRIDGE

I HAVE a very full understanding of the responsibility I have assumed, in accepting the great honor you have accorded me, in electing me your President

I am acutely aware of my own inadequacy to meet the standards set by my illustrious predecessors in this office. However, humility is a solid foundation for virtue, and the very realization of my limitations is a challenge to my sense of pride, so I put all my fears behind me, and assure you I am entering upon my new duties with a spirit of determination and enthusiasm which, with your help, will overcome what at first seemed to be insurmountable handicaps.

I know eulogy is distasteful to Dr. Hartwell, because he has told me so, nevertheless, I cannot refrain from saying a word about him tonight. I have spent some time recently, studying the history of the Academy. All of the addresses of its Presidents, up to and including 1879, that are to be found, and many of those delivered since then, I have read, so I have acquired knowledge, not only of the authors of those addresses, but also of their opinions of their contemporaries.

I have known Dr. Hartwell as a man, as a friend, as a patient, and as a physician, I have known him also as President of the Academy and as its Director, so I speak with authority, when I tell you that in all its ninety-odd years of existence this Academy has never had a person connected with its organization who has given to it more of himself and given to better advantage.

He has taught me many things that cannot be learned from books. He has always had the capacity for making friends. In him you find kindness, truth, patience, and honor. He has been a wise and inspiring leader. We are going to miss him, but, long after our generation has passed on, his spirit will continue to live in the affairs of the Academy, more indestructible than its walls, and vastly more precious.

Nearly a hundred years ago, on the evening of November 18, 1846, at the Fourth Annual Dinner of the Society for the Relief of Widows and Orphans of Medical Men, held at a restaurant on Broadway, near

\* Delivered January 5, 1939 at the Annual Meeting of the Academy.

Prince Street, the idea of an Academy of Medicine was born. This was indeed the horse-and-buggy age, not only of medicine, but of science in general. Let me remind you that the population of what is now the Greater City of New York was in the neighborhood of six hundred thousand, the first railroad train drawn by a steam locomotive, the first Atlantic crossing of a steam-propelled ship, and the use of illuminating gas as a means of street-lighting had been introduced but a few years before the founding of the Academy, while the first commercial telegraph line in this country was operated between Washington and Baltimore in 1844. Oliver Wendell Holmes reported the infectious nature of puerperal sepsis in 1843, and three years later, but a single month before the birth of the Academy, William T. G. Morton demonstrated the administration of ether to a patient on whom John C. Warren was about to operate, in the amphitheatre of Massachusetts General Hospital.

The prime motive for the formation of the Academy was not at this time the advancement of medical science, but rather the formation of a code of ethics to regulate the professional conduct of its members. The original Constitution, adopted January 6, 1847, reads, under Article 2: "The objects of the Academy shall be

"First. The separation of the Regular from Irregular Practitioners.

"Second. The association of the Profession Proper for purposes of mutual recognition and fellowship.

"Third. The promotion of the character, interests, and honor of the fraternity, by maintaining the union and harmony of the regular profession of the City and its vicinity, and aiming to elevate the standard of Medical Education.

"Fourth. The cultivation and advancement of the Science by our united exertions for mutual improvement, and our contributions to Medical Literature."

So we see the Academy was originally started not primarily as an institution for the benefit of mankind, but rather as an organization of one hundred twenty-one medical men whose chief aim was to draw the line sharply between regular practitioners and those whom they regarded as charlatans and humbugs.

The Standing Committees under the original Constitution were appointed by the President and were 1. Committee on Admission, 1. Committee on Finance, 1. Committee on Medical Ethics, 1. Committee on Publication, and 1. Council of Appeal—in keeping with the objectives

stated in the original Constitution

A year later, however, the order of the stated objects was changed, so that the cultivation and advancement of the Science, by united exertions for mutual improvement, and contributions to medical literature was placed in the leading position, while the separation of regular from irregular practitioners was relegated to third place

In 1874, the "Promotion of Public Health" was added to the objects of the Academy

Throughout the first twenty-eight years of its existence, the Academy of Medicine had no home. During most of this time, its small collection of books had no permanent resting place. On the occupancy of a building at 12 West 31 Street, in May, 1875, the Academy finally had a roof over its head. There were available for the Library four hundred volumes, and in June, 1875, a Committee on Library was added to the Standing Committees. From the time we occupied our first home up to the present time, we have been leaders in matters which affect public welfare and medical education. The Library increased rapidly in size until there were nine thousand volumes on its shelves in 1879, and twenty-five thousand in 1885.

The greatly beloved Abraham Jacobi had the vision, in 1885, to point out that the people would soon learn to rely on the knowledge and public spirit of the profession, and, as it depended on the Bar for legal advice, would consult the medical profession for sanitary necessities.

About this time, a bill was presented to the Legislature, ordering a Board of Examiners to institute State examinations, and a department to license practitioners of medicine, and the Academy of Medicine was the motivating force in finally securing such legislation.

Continued rapid expansion produced the need for larger quarters, and on November 20, 1890, a new building was opened, at 17 West 43 Street. Oliver Wendell Holmes is reputed to have said, in a letter of regret, written for this occasion, "Academies have been too often thought of as places of honorable retirement and dignified ease, roosts where Emeritus Professors and effete men of letters, once cocks of the walk, could sit in quiet rows while the fighting, the clucking and the crowing were going on beneath them. But the Academy which fulfils its true function is a working body. It deals with living subjects, it handles unsettled questions, it offers rewards for meritorious performances and sits in judgment on the efforts of aspirants for distinction. It furnishes

the nearest approach we can expect to a fixed standard of excellence by which the work of new hands and the new work of old hands can be judged. There are a certain number of squinting brains, as there are of squinting eyes among every thousand of any population. We trust it will always be enough for a physician to be able to say 'I am a Member of the New York Academy of Medicine!'"

A few years later, on January 22, 1897, the semicentennial was celebrated. The list of the accomplishments of the Fellows of the Academy during its first fifty years is too long to enumerate in its entirety, however, they fought for the improvement in the preliminary education of matriculants, for State examination as a standard of license to practise, for increase in the duration and number of college courses and medical school inspection, they agitated for new factory laws in behalf of women and children, for clean streets, for improvement in tenement house conditions, school houses, Reception Hospital, reformation of quarantine for the Port of New York, water supply for the city (Croton water and watershed), establishment of the Metropolitan Health Board of the city, protection of the Port of New York and the city against invasion by cholera, and for the establishment of free baths. In fact, to quote directly from Dr. Jacobi's semicentennial oration, "The responsibility toward both the public and the profession was always deeply felt by the Academy. What I could say, fragmentary though it be, should have convinced you that the best individual and collective efforts of the profession, as represented in the Academy, are being spent in the *service of the community* [The italics are mine]

"See to it that no personal interest, vanity, or misapprehension interfere with the progress of medicine. It is through our own efforts that we overcame the lack of knowledge on the part of legislators and the opposition of medical schools, when we enforced a certain amount of preliminary education and the establishment of State examinations. See that these, your gains, for they are yours, be not taken away from you, they were conquered in your behalf."

Lots on 43 and 44 Streets, directly adjacent to the Academy property were purchased in 1910, because of the steady and rapid growth of the Academy's activities and Library.

The majority of us are familiar with the recent history of the Academy. To the Standing Committees on Admission and Library have been added the Committees on Public Health Relations, Medical Education

Sections, and Fellowship, and just tonight, Medical Information With new problems, new responsibilities have developed, which, up to the present, we have met We moved into this building in 1926, and we have since had to build an addition for the rare book room and much needed office space Our Library, now over two hundred twenty-four thousand books and periodicals, is growing rapidly, and we shall soon need considerable additional stack room We are now the fourth medical library in the world, in point of size, and second only to the Army Medical Library in Washington on this hemisphere

I have attempted to give you a brief outline of our history, as we approach our hundredth anniversary It is a story of continued progress There are, among our Fellows, those who think we have expanded too much and should curtail our activities We must admit that these are troublous times, but, for my part, I am strongly in favor of continuing to be true to the traditions and ideals which have become our established principles

During my term of office, I should like to see a quickening interest in Academy affairs evinced by a much larger proportion of Fellows and Members, especially of the younger group, for excellence in any department can be procured only by the labors of a lifetime

It is my hope that we may stir the consciousness of the public to the significance of the Academy as a public health counsellor We must continue our growth, Foundations have helped us appreciably because of the scope of our activities in behalf of the physician and of the public, we have an obligation to those Foundations, to keep faith with them, by carrying on in the same direction, and we have an obligation to the people, to keep faith with them, by carrying on, as they have learned to rely on us to do

The obligations we have accepted and discharged carry with them reciprocal responsibilities We are, after all, in the same position as other institutions of learning, both special and general, such institutions are constantly appealing for help, to maintain the forward progress of their work We want to be in position to do better work, to meet increasing demands upon us If we do not continue to progress, we shall not remain static, we must inevitably give up many of the things which are so important to the community at large What we have already accomplished, we have just reason to be proud of, but from whence we came and where we are is not nearly so important at this juncture as whither we are going

## HEAT LOSS FROM THE HUMAN BODY\*

*Harvey Lecture, December 15, 1938*

EUGENE F DU BOIS

THE Harvey Society was founded thirty-three years ago by a small group of scientists who were interested in stimulating the development of medicine, physiology, and allied subjects. One of the leaders, the man perhaps most closely identified with the Society, was Graham Lusk. To his desk in the old building of the Cornell Medical College came investigators from all parts of this country seeking advice and inspiration regarding their problems. He was interested in many phases of metabolism, but the controversy he loved most intensely was that which centered about the relationship of the basal metabolism to the surface area. It was this that inspired our studies on radiation, convection, and vaporization and the general campaign was planned by Graham Lusk shortly before his death in 1932 which checked but certainly did not end the influence of this great leader and rare spirit.

Graham Lusk paid a great deal of attention to heat loss as well as heat production. Between 1910 and 1933 most students of the respiratory metabolism concentrated on heat production. Since 1933 several groups in this country and Europe have made intensive studies on heat loss. There is a dispute as to which is the better viewpoint reflecting in a rather amusing manner the constant struggle that is taking place in the body between heat loss and heat production. At certain times of the day heat production is predominant and heat loss does its best to catch up. At other times of the day heat loss is the controlling factor. This can be illustrated by a diagram which shows the curve for a twenty-four hour period of heat production and heat loss in one of the men who works in our laboratory (Fig. 1). These curves were constructed partly by temperature measurements and estimations as to activity. They are, therefore, semi-diagrammatic. The solid line gives the approximate heat production, the dotted line the heat loss.

\*From the Russell Sage Institute of Pathology in association with the New York Hospital and Department of Medicine, Cornell University Medical College.

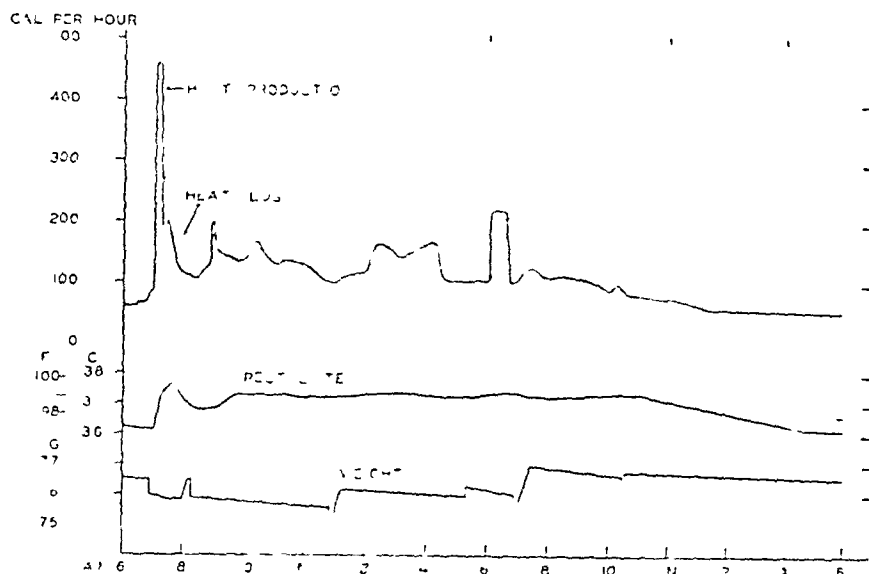


Fig 1—An estimation of the variations which occur in the daily life of control D, obtained partly by direct measurements on several days and partly by estimation from calorimeter experiments on other days. The subject runs in the Park at 7 00 a m daily. The other peaks in the curve of heat production occur when he travels from his home to the laboratory in the morning, engages in the usual hospital activities, and walks home in the evening. The variations in weight are caused by meals, voiding, insensible perspiration, etc.

The day selected for the experiment was in the winter time and started at six o'clock in the morning with the man asleep in bed in a cold room. The rectal temperature was low. Heat loss and heat production balanced. At seven o'clock he got up, dressed, and ran one and one-quarter miles before breakfast. His basal metabolism was increased approximately six-fold, the heat loss was increased only four- or five-fold so that a considerable amount of heat was stored in the body with a resultant rise in the rectal temperature. While he was dressing and taking breakfast, the heat loss exceeded the heat production and the rectal temperature fell. The curve for the rest of the day showed the variations resulting from the walk to the laboratory, work, lunch, and the walk home followed by dinner, modified by the man's reactions in changing his clothing, opening windows, and other processes. During the night when he was asleep in a cold room, heat loss seemed to assume the dominant role. He did little or nothing to control the situation, and if his basal metabolism had not been set at a certain level he would have been as cold as a corpse before the night was over.

## FACTORS INCREASING

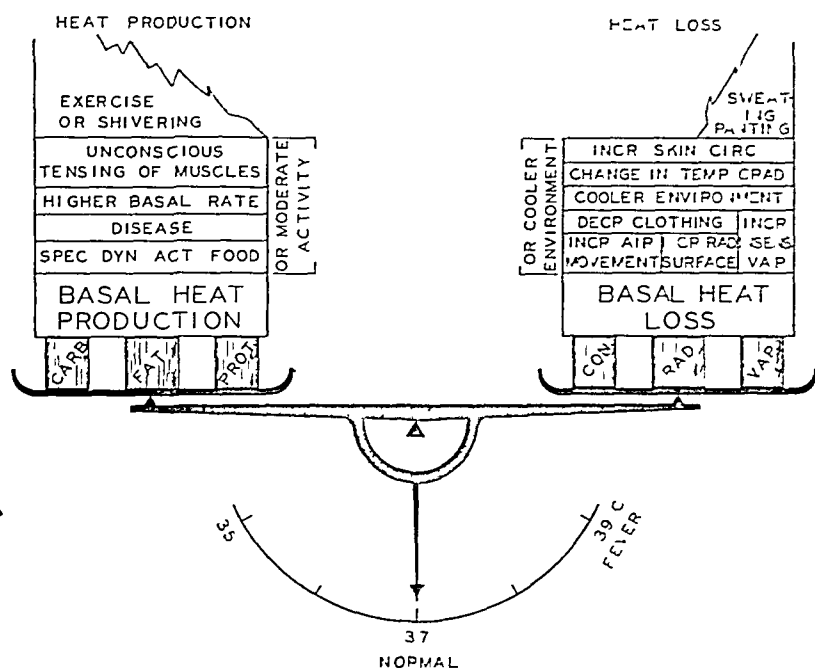


Fig 2—Balance between factors increasing heat production and heat loss

Another diagram (Fig 2) which summarizes the whole situation is introduced at this point to bring out the multiplicity of factors. Heat production is placed on one pan of the balance, heat loss on the opposite pan. When the man is quiet in a warm room the basal heat production and loss equal each other and the body temperature is at its normal point of  $37^{\circ}\text{C}$ . When any other factor is added, the balance is temporarily altered until an equal addition on the other pan restores equilibrium. Heat production takes place only through the agencies of the combustion of carbohydrate, fat, and protein, heat loss through radiation, convection, and vaporization. When any one of these three factors changes on one side of the balance there is a readjustment of the other two factors. The details of these adjustments form the basis of this discussion. The major part of the problem is purely physical, but the conditions are frequently altered by physiological changes and it is impossible and perhaps unimportant to make any sharp distinction between physics and physiology. It is well however to consider first



the body as a physical mass with an average internal temperature of  $37^{\circ}\text{C}$ , slightly warmer than this in certain organs. Since the body contains considerable amounts of fat and bone with low capacities, its specific heat is about 0.82, and a man weighing 70 kg is thermally equivalent to 57 kg of distilled water. The surface of the man is encased in a layer of skin and subcutaneous tissue which is unusually efficient as an insulator against heat or cold. The specific conductivity of cork is 0.0007 gm cal/sec/cm<sup>2</sup>/cm, epidermis, subcutaneous fat and muscle tissue are slightly better insulators with conductivities between 0.00047 and 0.0005. The actual surface, as I shall explain later, is almost a perfect radiator or "black body" in the language of the physicist. On account of the configuration of the human body the surface area is large, for a 70 kg man, about 1.8 square meters. Within 1 cm of the surface of such a man there is a mass of tissue which weighs about 15 kg, about one-fifth of the total weight. When a naked man is exposed to an atmosphere of  $22^{\circ}\text{C}$  ( $72^{\circ}\text{F}$ ) there is a constant loss of heat through the surface which assumes an average temperature of about  $30^{\circ}\text{C}$ . This means that there is a gradient from the interior of the body to the surface, on an average 1.8–2.5 cm deep, but it may in some places be as great as 10 cm. Inasmuch as the extremities have relatively small diameters and are situated at a considerable distance from the central heating apparatus of the body, their temperatures under cool conditions are considerably below the temperature of the central mass. In addition, the surface of the body is constantly moist, even when there is no activity of the sweat glands. Water from the moist interior seeps through the epidermis.

Of course man is more than such an inert mass of physical components. There is a constant production of heat in his muscles and organs. This heat is transferred to all parts of the body by means of the blood stream, warm blood coming from the muscles and the organs, cooler blood from the surface, producing relatively colder streaks as it passes through the veins of the extremities. In addition, there is a beautiful system of control of the blood flow to the surface so that the body can, when it is too cold, change the skin into a suit of clothes just as efficient as wool or cork. When the need for increased dissipation of heat arises, the body can pour quantities of blood into the deeper layers of the skin so that the inner side of the epidermis attains a temperature equal to that of the warmest portions of the body. At the same time

when the sweat glands pour out water, it can keep the surface moist enough to permit huge losses. Every gram of water vaporized from the surface of the body withdraws 0.58 calories through the latent heat of vaporization. Also, the body can change its heat production from a basal level of say 60 calories per hour to a level of more than 800 calories per hour by means of violent muscular exercise.

The skin is an organ beautifully adapted for its purpose. The tough epidermis is perforated by sweat glands, and beneath the Malpighian layer there is a rich plexus of capillaries, arterioles, and venules so that there can be a tremendous increase in the blood flow. Moreover, the skin is provided with sense organs for heat and cold, having a delicacy which was not suspected until Hardy and Oppel<sup>1</sup> proved that the skin of the forehead could detect changes of  $0.003^{\circ}\text{C}$  in three seconds when exposed to heat, with slightly lower sensitivity when exposed to cold.

MODE OF HEAT LOSS	TEMPERATURE OF SURFACE OF BODY	TEMPERATURE OF SUR- ROUNDING OBJECTS OR AIR	AREA OF SURFACE OF BODY	CHARACTER OF SURFACE	SPECIAL FACTORS
	$T_s$	$T$	$A$	$E$	
RADIATION	$\frac{T_s^4}{(T_s)^4}$	$- T^4$	85% EFFECTIVE	99% BLACK	
CONVECTION	$T_s$	$- T_o$	100%	SMOOTHNESS	AIR MOVEMENT
VAPORIZATION	PERSPIRATION VAPOR PRESSURE $T_s$	HUMIDITY VAPOR PRESSURE $T$	100% FOR SEEPAGE + RESPIRATORY PASSAGES	% WETTED BY SWEAT + RESPIRATORY ACTIVITY	AIR MOVEMENT

Fig. 3—Simplified expression of laws of heat loss.

The importance of the surface area of the body is clearly brought out in Fig. 3 which is a simplification of the rather complex physical formulas for heat loss by radiation, convection and vaporization. Newton's Law of heat loss considers only radiation and convection. Radiation is proportional to the temperature of the surface of the object minus the temperature of the surrounding objects or air multiplied by the surface area, corrected for the character or physical blackness of the surface. In the case of convection air movement is of prime importance but this does not affect radiation. For radiation the Stefan-Boltz-

man Law is more accurate, involving the fourth powers of the absolute temperatures of the surface and of the surrounding objects. These figures are obtained by finding the levels above the absolute zero,  $-273^{\circ}\text{C}$ . For small differences such as we are discussing, the simple Newton Law is sufficiently accurate.

Vaporization is more complex, depending on the difference between surface temperature and air temperature, or rather on the difference between the vapor pressure of the air immediately in contact with the slightly moist skin and the vapor pressure of water in the surrounding air, which is the expression of its humidity. Air movement is an important factor. Under ordinary conditions, about two-thirds of the water vaporized comes from the whole surface of the skin, one-third from the respiratory passages. The depth and frequency of respirations may become factors though they are not especially important.

It will be noted that each one of these modes of heat loss is proportional in some way to the total surface area of the body and this applies with modifications to all warm-blooded animals, birds as well as mammals. I have not time to go into the question of the surface area law but I shall refer you to Benedict's book on *Vital Energetics*<sup>2</sup> which compares calories per square meter of body surface for a large number of warm-blooded animals. Most of these show approximately the same level of basal metabolism per unit of surface area. A few are quite far off the line. I do not know where or when the various species of animals were given their basal metabolism. Perhaps Noah did it when they left the Ark. I suppose that the reason he could not do a uniform job with the animals was because he did not have scales small enough for the dwarf mice and large enough for the bull, the horse, and the elephant. The subject deserves more study.

There are a few minor heat losses which should be mentioned. The warming of food and drink is relatively unimportant. Conduction (*Leitung* of the Germans) or the transference of heat through solid objects is a factor if a man lies on the cold ground. Locally it becomes manifest when one touches a metal object and heat is transferred so rapidly from the skin that the object feels much colder than its non-metallic surroundings which are at the same temperature. In most of the older physiological literature the term conduction apparently includes heat loss by convection. I searched many of the textbooks of physiology before I found any mention of convection.

In our experimental procedures we have reduced conduction until it is practically zero. Heat lost in warming the air from the lungs has been added to the convection from the surface of the body and the vaporization from the lungs measured together with the vaporization from the skin.

When we made our first calorimeter experiments we were under the impression that radiation was the most important channel of heat loss. Later we discover that it is important chiefly under basal or quiet conditions. Still it is a constant factor deserving of much more attention than it has received.

The study of heat loss is probably as old as the hills. In a previous highly scientific publication I was able to prove that the main facts were discovered in the Garden of Eden by Adam and Eve within twenty-four hours of their creation. They probably learned a good deal more when they took to clothing and manual labor. Civilized man has developed a good practical knowledge of the subject, not quite as good as that of the Eskimos who are still in the early Stone Age. I suppose Newton was the man who did most on the subject of heat loss. It was Rubner who first grasped the real significance of the subject as far as man was concerned. He published in 1896<sup>3</sup> a table giving the measured or estimated radiation from a man producing 2700 calories a day, together with the estimated losses from convection, radiation, and the warming of food, and this is about the only table that has been published in the textbooks. His methods are not stated, but he grasped the essential points and made allowance for the fact that radiation does not depend on the total surface of the body but rather on its profile surface according to Lambert's Law. There is, for example, no loss of heat by radiation in the axilla or between the legs. Rubner's table of the partition of heat loss applied only to the special case of a man who was active enough to produce 2700 calories a day under special atmospheric conditions. His data were probably faulty, but Rubner was a genius who could draw correct conclusions from inaccurate and incomplete data whereas most of us draw incorrect or incomplete conclusions from data that are accurate.

Lefèvre<sup>4</sup> in France was a pioneer in this field of heat loss. In more recent years Cobet and Bramigk<sup>5</sup> and Bedford and Warner<sup>6</sup> have made good use of radiometers. The work that we found of most help was contained in the neglected publications of Aldrich<sup>7</sup> of the Smithsonian

Institute He studied the surface temperature, radiation, and convection of school children but his instrument was rather bulky and slow The long series of studies by Bohnenkamp<sup>8</sup> and his associates in Grafe's clinic in Wurzburg have been most stimulating Bohnenkamp was really the first man to emphasize the importance of the profile or effective surface area in relationship to radiation and this effective surface which amounts to 80 to 85 per cent of the total surface has been appropriately called the "Bohnenkamp surface" He brought out a good deal of evidence to show that heat loss as determined by effective surface area is a factor in setting the level for heat production His radiometer had several faults of construction and many critics have pointed out errors in his work, focussing their attention on these errors rather than on the stimulating originality and significance of his main conclusions

Since we have been engaged in our own studies several important publications have appeared Burton<sup>9</sup> working with a calorimeter in Murlin's laboratory in Rochester has used a jacket made of resistance wires to measure the changes in skin temperature and has drawn valuable conclusions regarding the temperature gradients and the surface of the body Winslow, Herrington and Gagge<sup>10</sup>, using the splendid equipment of the Pierce Laboratory in New Haven, have been able to study the heat losses under a large variety of environmental conditions, securing wide differences between the relative proportions of radiation and convection Their work has been characterized by a careful analysis of all the physical factors They have brought out the conception of operative temperature and degree of wetness of the body, and they have developed the study of the conductance of the skin Their papers will serve as a basis for the scientific study of air conditioning

Time does not permit more than a superficial review of the literature with all of its ramifications For example, it is impossible to cover the studies of Benedict and Carpenter of the Nutrition Laboratory in Boston who have been publishing on the subject of direct calorimetry since the days of the first Atwater-Rosa-Benedict calorimeter and have made valuable contributions on the subjects of skin temperature and heat loss by vaporization The work of Bazett, McGlone and Burton<sup>11</sup> on the temperature of the muscles and subcutaneous tissues and temperature gradients is of fundamental character The heating and ventilating engineers, especially Houghton, Sayers, Yant and Yaglou of the U S Bureau of Mines and Barker of England, have made studies of the

subject from a theoretical as well as a practical standpoint Levine and Gordon and their associates<sup>12</sup>, working first at the Nursery and Child's Hospital and later at the New York Hospital, by means of exceedingly careful and detailed studies, are furnishing the data for heat loss of small children, a field of clinical as well as theoretical importance Hick, Keeton, and Glickman<sup>13</sup> in Chicago are making many studies of various physiological manifestations at different temperatures Deighton<sup>14</sup> in 1933 wrote an excellent review of physical factors in body temperature and heat elimination Perhaps the best work on the subject, a work too much neglected, is that of Leonard Hill<sup>15</sup> published in 1916-1919 Many of the points that he brought out in these publications are being rediscovered at frequent intervals

Graham Lusk and his associates in the Department of Physiology of Cornell University Medical College have contributed a long series of papers on animal calorimetry starting in 1912 The Russell Sage Institute of Pathology, of which Graham Lusk was the Scientific Director, had been working since 1913 with an Atwater-Rosa-Benedict respiration calorimeter which measured heat production by the methods of indirect and direct calorimetry The indirect or chemical method gave the total heat production with the details regarding the proportions of protein, fat, and carbohydrate oxidized every hour The direct method gave independently the calories lost in vaporization and lumped together the calories of radiation plus convection The sum of these, corrected for calories stored in or lost from the body, indicated the total heat production, using physical rather than chemical measurements In the long run the two methods checked satisfactorily and served as an indication of mutual accuracy The calorimeter was employed for nineteen years, chiefly in a study of heat production, but about 1931 we developed a great curiosity regarding the mechanism of heat loss, having published some data which were difficult to explain For example Barr and Du Bois<sup>16</sup> in 1918 in the study of malaria had stated that it was possible for the skin to give off more heat when it was cold than when it was warm This seemed to be a violation of Newton's Law of cooling, and it brought forth a number of stinging comments which could not be dodged After all we knew very little about the partition of heat loss from the human body Heat, perhaps the most important end product of metabolism, had been neglected because there was no satisfactory method of dividing radiation from convection

range of wave lengths from the very short cosmic rays and x-rays on the left to the long infra-red and radio waves on the right. The radiation from the sun as shown in the highest peak starts in the ultraviolet reaches its maximum in the visible range, and is shut off by the earth's atmosphere a short distance below the red at a wave length of about  $2$  to  $3\mu$ . The radiation from a red hot stove begins in the red and extends into the far infra-red. The human body has a much lower temperature and therefore its emissions have wave lengths which fall between  $5$  and  $20\mu$  with a summit of about  $9\mu$ . These waves are stopped by many substances, such as glass, through which the sun's rays penetrate with ease. They fly outward with the speed of light in straight lines.

From the standpoint of radiation a "perfect black body" is a substance which reflects no rays, transmits no rays, but absorbs them all, or, if the heat be travelling in the opposite direction, radiates them all. In the visible range such objects necessarily look black to the eye but when it comes to the infra-red, color does not count. Hardy and Muschenheim<sup>15</sup> in this range found no essential difference between the skins of white men and coal black negroes. In a dark room in the middle of the night we are all black.

They found that human epidermis, even in layers that are extremely thin, blocks off almost completely the passage of infra-red rays longer than  $3\mu$ . The human skin comes within 1 or 2 per cent of being a perfect infra-red black body radiator. This confirms the findings of the majority of previous investigators and refutes some of the more recent work. The blackness of the skin is of considerable physiologic importance and it is particularly fortunate for the investigator since it enables him to calculate skin temperature from radiation.

The surface involved in the measurement of radiation is the profile or "Bohnenkamp surface" which in the case of a man in military or mummy position is very close to 80 per cent of the total surface as measured by the Sage Height-Weight formula. When a man squats with his knees close to his chest he can reduce his effective surface until it is only 55 per cent of the total surface.

One of the most important factors is the surface temperature and the literature on this subject is enormous. Many years ago G. N. Stewart pointed out that it was easy to measure the skin temperature but that it was hard to know what to do with it. Dr. Hardy has said and proved that it is very difficult to measure skin temperature but easy to know

what to do when you have it. In a series of careful experiments he demonstrated that the commonly used surface thermometers which are partly in contact with the skin and partly in contact with air or solid substances are subject to many errors. His method of using a radiometer to find the skin temperature without touching the skin is now generally accepted as the only method that gives absolute readings, although the other instruments may indicate differences with sufficient accuracy for clinical purposes. Dr. Hardy's applications of his exact measurement of skin temperature are so numerous that they would fill many chapters. Suffice it to say that they form the foundation of this report.

Just as important as the temperature and radiating properties of the skin are the temperature and character of the objects towards which the body radiates. In most rooms the air and walls are at the same temperature and the walls are fairly good black bodies. In many rooms there are spots of heat on radiators and spots of cold at the windows. Winslow, Herrington and Gagge<sup>10</sup> have made use of a combination of cool air and cool polished walls which reflect radiation from an electric stove. The experimental subject sits in a comfortable chair surrounded by polished copper walls, and the stoves reflect, from the polished copper, radiant heat without materially raising the temperature of the air. The New Haven investigators have been able to make a series of studies with the different radiating temperatures and have ingeniously calculated the "operative temperature" under many conditions.

Convection depends chiefly upon the rate and character of the movement of the air over the surface of the body. The flow may be uniform or turbulent, steady or intermittent. Losses by convection increase rapidly with the rate of movement of the air, but Leonard Hill<sup>11</sup> has shown that after a certain point the curve flattens. With speeds greater than 30 meters a second, approximately 70 miles an hour, there is no greater loss of heat through convection because the particles of air move so fast that they do not have time to take up more heat. Hill points out that this may be some consolation for motorists. In spite of the general belief to the contrary, the humidity of air has practically no effect on the loss by convection and metal objects lose heat at the same rate whether the air be humid or dry. With animals humidity would affect convection secondarily because it modifies vaporization and dampness probably makes the clothing or fur a better conductor of heat.



The study of perspiration is fascinating and Kuno<sup>19</sup> of Japan has written a book in English on this subject. Inhabitants of northern climates possess two or three million sweat glands, those who dwell in the tropics about a million more. On the hands, feet, and axillae there is a continual slight activity of the glands. Over the rest of the body the eccrine sweat glands are called into action when needed to dissipate heat. There are some areas, such as the palms of the hands and soles of the feet, which respond promptly to emotion but lag behind when the rest of the body is trying to lose calories. The apocrine sweat glands in the axillae and pubic regions are a good deal of a nuisance because they secrete those specific aromatic substances which contribute more than their share of body odor. The eccrine glands over the rest of the body are man's safety valves in hot weather and there is no one human attribute of more importance than the ability to sweat skilfully.

In cold weather the humidity of dwellings is always low and there is such a large gradient between the vapor pressure of the skin and air that vaporization is rapid. Even a large rise in the percentage humidity of a room at 20° C (68° F) makes very little difference in vaporization, and after all, vaporization at this temperature accounts for only one-quarter of the total heat loss.

I have reviewed the fundamental laws of heat loss in the light of our present understanding but I must confess that when we started work there was a great confusion in the literature and in our own minds. It was only as we progressed from experiment to experiment and compared our results with those of others that the subject became relatively simple. We have been forced to change our views many times and are fully prepared to change them every year. It was in 1932 that the Russell Sage Institute of Pathology moved its calorimeter to the New York Hospital where a room had been provided with adequate temperature control. In 1934 the radiometer had been fully tested and we were in a position to make the first studies in which heat production, total heat loss, radiation, convection, vaporization, surface temperature, and storage of heat in the body could be measured accurately.<sup>20</sup> We were confronted with many variables and decided to reduce them to a minimum. In order to keep heat production constant it was necessary to work with subjects under basal conditions. In order to measure surface area and skin temperature we decided to use naked subjects. In order to eliminate conduction we employed a bed made of fish line, using a

small folded sheet under the hips and shoulders and a small towel under the head. Since the men were lying close to the bottom of the calorimeter and the currents of air were directed across the top, convection was reduced to the lowest possible level. The velocity of air near the surface of the body was too small to be measured by delicate anemometers or appreciated by the skin. There remained, however, a natural convection current due to the warming of the air by the man's body. It is necessary to emphasize these points because other observers have used patients after food intake and in different positions. Any such departure from the basal, causes wide differences in the results.

Our main studies were made on two normal men and three normal women, supplemented by a small number of experiments on other normal controls including nudists.

The routine for the day was as follows. The subject of the experiment came to the laboratory about nine o'clock, having eaten no food since the previous evening. He sat in the calorimeter room at the experimental temperature for about an hour, and then as he undressed surface temperature readings were made at twenty different areas on the skin. He was then weighed and his height measured so that we could calculate surface area. Next, he was placed on the calorimeter bed, the electrical thermometer inserted 12 cm. into the rectum, and the radiometer hung on the inside of the calorimeter. About eleven o'clock the box was sealed and the preliminary period started. About twelve minutes before twelve o'clock, after an equilibrium was established, the man was instructed to start the second series of the skin temperature readings. This he accomplished by pointing the radiometer at the same twenty spots of the surface. These measurements required about two minutes and involved the expenditure of 1 to 2 calories. Next followed a quiet period of ten minutes, and the first experimental period was started at about noon. During the first hour the man lay motionless. At one o'clock this basal period was terminated and a transition period of twenty to thirty-five minutes started at the beginning and end of which we measured surface temperature once more. This was sometimes followed by a second basal hour, but in a good many experiments a new factor was started in the transition period such as moderate work or the use of the electric fan. In the colder experiments the procedure was modified so that the transition period accommodated itself to the spontaneous chill. The subjects became very skilful in giving us a warning

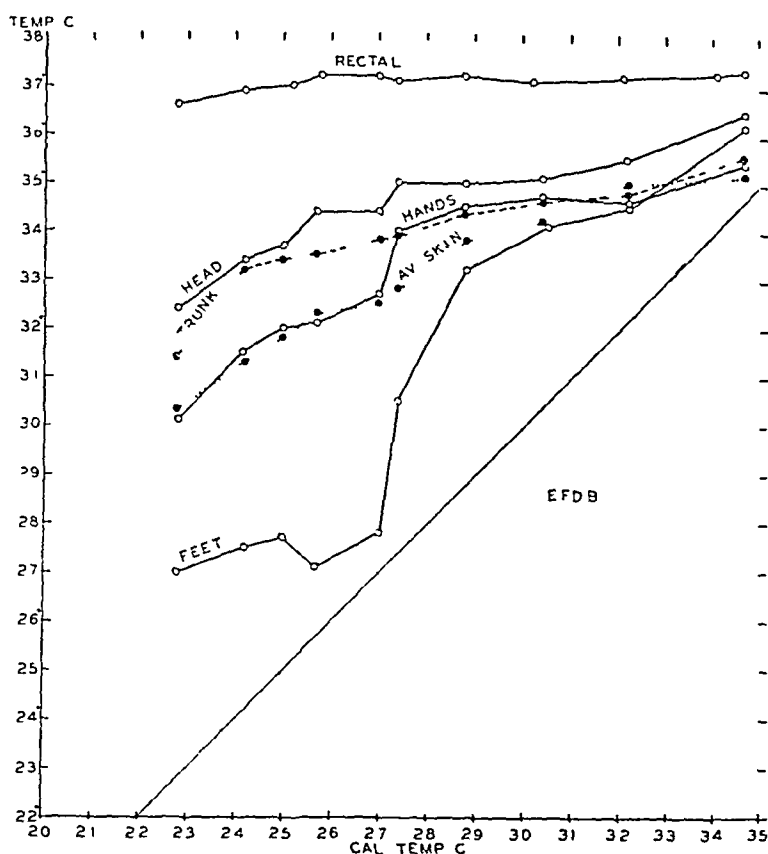


Fig 6—Skin and rectal temperatures of subject D, during his experiments at different environmental temperatures

about ten minutes before the chill became inevitable. After the third period, terminating about 2:30 p.m., we measured surface temperature once more, and the man was taken out of the box and given a much needed breakfast.

The first problem was to determine the basal heat production and heat loss over the greatest possible temperature range. We could not use room and calorimeter temperatures higher than 36° C (97° F) because the sweating would be too great for us to measure accurately in our calorimeter. We could not go below 22° C (72° F) because it was impossible for the man to remain quiet long enough before having a chill. This is ordinary room temperature, and it does not seem cold to us who are clothed and moving about, but it does feel cold when you are lying motionless with an empty stomach and a naked body. Even trained artists' models and nudists shiver under these conditions.

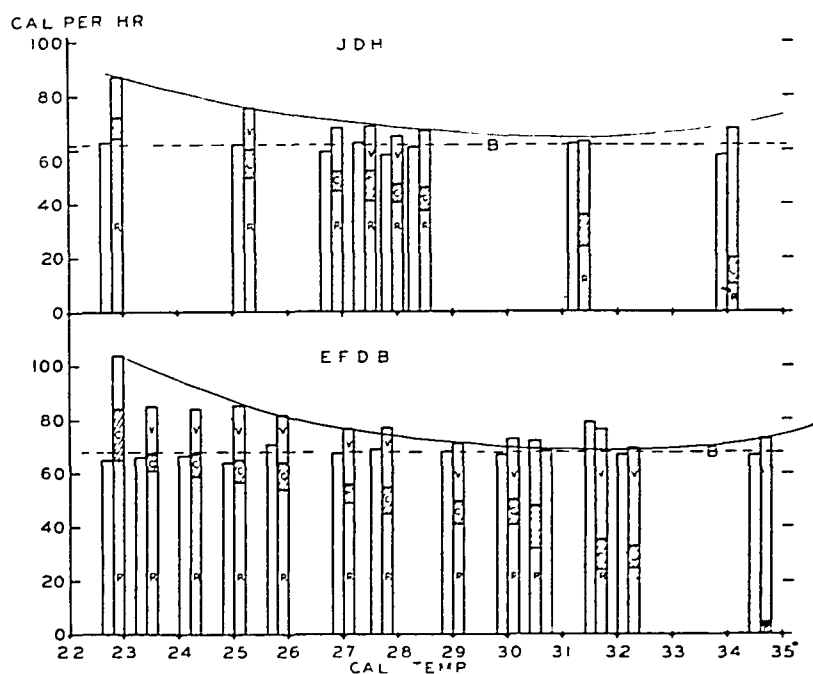


Fig. 7—Changes in heat production and heat elimination for two male subjects during the basal periods with increasing calorimeter temperatures. Blank columns on left heat produced; columns on right heat eliminated. V, vaporization; C, convection; R, radiation.

Having secured the basal metabolism in the first experimental period it was easy to add for comparison the other factors previously mentioned. The basal periods were fairly simple, but when it came to chills everyone was busy, almost as busy as the man who was having the chill. Personally I find it much easier to have a chill than measure one. When the experiment was over it required a particularly long series of calculations to determine radiation. It was necessary to find the average surface temperature and effective surface area of each part of the body. Fig. 6 gives the average temperature for one of the men measured after he had been lying naked and motionless for 2 to 3 hours. The straight diagonal gives the air temperature; the top line the rectal temperature. In the warm zone of 34°C (93°F) all temperatures are within 2.5 degrees of each other. In the cold experiments the differences are great and the temperature can fall in large masses of body tissue without materially affecting the rectal temperature. The feet are almost

as cold as the surrounding air. In fact, the surface of the toes is usually 1 or 2 degrees below air temperature. Their constant moisture causes excessive cooling. They look and act like good radiators.

Fig. 7 gives the results on the two men who have been studied at frequent intervals in the calorimeter. The first blank column for each experiment represents heat production as measured by oxygen consumption. It will be noted that the basal metabolism was surprisingly level with no sign of Rubner's "chemical regulation." Even at the coldest temperatures it did not rise until about five minutes before a frank chill. The second columns show heat loss divided into radiation, convection, and vaporization. Inasmuch as radiation depended on the temperature difference between the surface of the skin and that of the walls, the heat loss by radiation diminished uniformly with rising temperature until it disappeared completely when skin and walls were at the same level.

Convection showed no marked diminution until  $32^{\circ}\text{C}$ . Like radiation it disappeared when the air was as warm as the skin.

Vaporization accounted for 18 to 20 per cent of the heat loss at the lower levels, 25 to 40 per cent in the middle zone, increasing rapidly above  $31^{\circ}\text{C}$  until it was obliged to take over 100 per cent of the heat loss at  $35^{\circ}\text{C}$ , since radiation and convection had fallen to zero.

The temperature range studied must be divided into three zones. The warm zone above  $30^{\circ}\text{C}$  is a region of discomfort because the skin is dripping sweat. The man is too hot and the balance between heat loss and heat production is made but poorly. There is a region between  $30^{\circ}\text{C}$  and  $28^{\circ}\text{C}$  where the heat loss is equal to the heat production. This is the so-called comfort zone, and it is comfortable because the body is able to make quite easily the physiological adjustments which maintain equilibrium. In the warm part of this zone the amount of blood flowing to the skin is so large that a great deal of heat is carried close to the epidermis. The sweat glands are not called into action. In the colder part of this comfort zone the blood flow to the surface is so greatly diminished that the skin has become as good an insulator as a suit of clothes.

Below  $28^{\circ}\text{C}$  is the zone where heat loss inevitably exceeds heat production if the man remain in the basal state. As the atmosphere grows colder, vaporization and convection remain about the same but radiation increases and there is nothing that the naked body can do to check this loss. At the lower limit of the comfort zone there had been a maximal

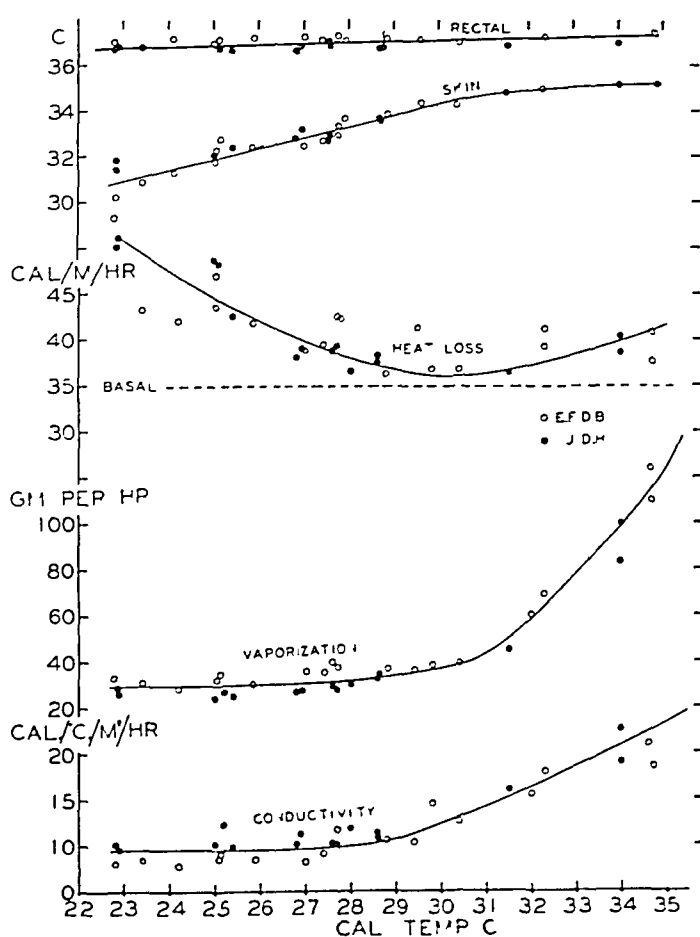


Fig 8—Changes in factors involved in heat loss regulation with increasing calorimeter temperatures

constriction of the subcutaneous vessels. The skin had become a suit of clothes but even a suit of clothes has its limitations. Below this level the living body loses heat like an inanimate object. Some people, especially trained nudists, boast of their ability to stand cold weather but nudists possess no magic that will interfere with the laws of radiation.

Fig 8 brings this out in a more graphic form giving once more the temperature range from 22 to 35°C. The top line shows the rectal temperature slightly lower in the cold zones than in the warmer. The skin temperature, however, is much lower in the colder zones with a curve which flattens out in air above 31°C. The heat loss is far above the basal heat production in the colder zone; the vaporization curve

makes a sharp break at the upper limit of the comfort zone about  $31^{\circ}\text{C}$ . The line for the conductance of the skin is the most interesting. Below  $28^{\circ}\text{C}$  it is practically straight and this means that throughout this region the skin has just the same conductivity because it is almost bloodless and acts like a dead insulator, slightly more efficient than cork. Above  $28^{\circ}\text{C}$  it is evident that a new factor has been added, transferring heat from the interior of the body to the surface and this new factor is, of course, an increasing amount of blood. The blood flow to the skin can be measured by this curve, and it has been found that with an environmental temperature of  $34^{\circ}\text{C}$  the cutaneous circulation may account for 12 per cent of the total cardiac output.

Last year in the Sage Laboratory, Dr. Hardy and Dr. Milhorat made a similar series of calorimeter observations on three healthy normal women of average build. They have kindly given me permission to discuss their results in advance of their publication. The rectal temperatures are the same as those of the two men, skin temperatures a little lower in the cold zone, higher in the warm zone. Basal heat production, much to the surprise of all of us was the same as that of the men in the colder ranges but dropped very markedly between  $28^{\circ}\text{C}$  and  $31^{\circ}\text{C}$ . Heat loss which was lower than that of the men in the cold zone showed exactly the dip in the warmer zone that had been evident in the basal metabolism. The conductance of the skin was lower than that of the men, as might be expected from the slightly greater amount of subcutaneous fat. The thermal loss or loss of heat per square centimeter of surface for each degree of difference between the skin and environment was absolutely uniform both for men and women throughout this range, demonstrating the fact that the experimental procedure possessed an accuracy that compared most favorably with that obtained by physicists working with inanimate objects.

This curious dip in basal metabolism in warm environments may be considered a type of chemical regulation, changing the metabolism without any change in the physical activity. There seems to be no question about it since the methods of direct and indirect calorimetry agree almost exactly. It may perhaps explain the reason that there has been so much uncertainty regarding the level of the average basal metabolism of women. After all, the differences between men and women shown in this chart are in accord with the general observation that women stand cold much better than men. Perhaps it also brings out the point known to the

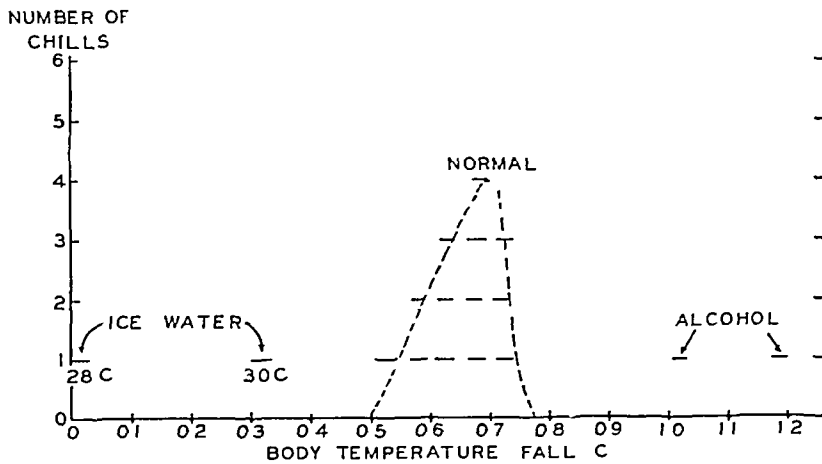


Fig 9—Diagram showing the fall in the average body temperature before the onset of a frank chill. Under normal conditions the chill comes after a drop of about 0.65° C. Alcohol postpones the chill, ice water in the stomach precipitates the chill.

ancients "*Vanum et mutabile semper femina*"

One of the most striking facts in these experiments is the great excess of heat loss over heat production in the colder atmospheres. Obviously the naked person exposed to air at 22 to 24° C cannot go on losing heat indefinitely. The body reacts with a chill which is purely involuntary. Thirteen such "normal chills" have been observed in our experiments in men and women (Fig 9). We calculate the average body temperature fall, giving a weight of 80 per cent to the mass of tissue measured by the rectal thermometer and the other 20 per cent to the superficial tissue represented by the average skin temperature. It is evident that these chills come with surprising regularity when the average body temperature has dropped two-thirds of one degree. This of course applies only to chill experiments with naked subjects under our experimental conditions. If a drink of 60 cc of brandy containing about 28 cc of alcohol be given the skin temperature is raised a little, the man feels warmer, and the chills are delayed until a fall in body temperature is almost twice as great. This may at first seem like a beneficial effect, but it should be considered as a serious and perhaps dangerous impairment of the temperature regulating mechanism. If instead of giving alcohol we substitute its mimic rival ice water we obtain a chill long before the chill would be due in the natural course of events.



We have studied in detail nineteen chills and have compared them with the chills of malaria and the chills following the intravenous injection of foreign protein observed by us twenty years ago in the same calorimeter. A sample chill shown in Fig. 10 followed a basal hour at an environmental temperature of  $23^{\circ}\text{C}$  ( $73^{\circ}\text{F}$ ). When the man came to the laboratory and undressed, his average skin temperature was at the usual level of  $33.5^{\circ}\text{C}$ . This dropped steadily during the preliminary period and first basal hour, the rectal temperature scarcely fell at all. Between 11 a.m. and noon his basal metabolism was at its normal level, about 60 calories, but inasmuch as the surface of the body was losing heat, the total heat loss was 28 calories greater than the production. The man felt no serious discomfort and no tensing of the muscles until 11:50 a.m., when he signalled that he felt sure a chill was due in about ten minutes. This gave us time to start another period in the calorimeter, and in a few minutes he experienced a paroxysm which shook the whole apparatus. This lasted twenty-five minutes and during the total period of thirty-six minutes the heat production was at the rate of 140 calories per hour, exceeding the heat loss by 43 calories. Most of this heat was stored near the surface, and the skin temperature rose distinctly with only slight change in the rectal temperature. After the chill the man felt comfortable, his heat production dropped to the basal level, but heat loss still remained high, the skin temperature fell abruptly, and he had a second chill a few minutes after the experiment was terminated. It is interesting to study the details of the heat loss in these three periods. The total loss was increased slightly during the chill and all of the increase could be ascribed to a rise in convection caused by the clonic movements of the body. Radiation was decreased because the skin temperature was lower during the chill than either of the basal periods. This is a confirmation of our much disputed statement made twenty years ago that the body could give off more heat through a cold skin than through a warm skin. Until we had the radiometer it was impossible to measure convection and none of us had the intelligence to realize the importance of increased air movement which would inevitably follow shivering.

The effect of moderate work is shown in the second diagram of Fig. 10, a sample of a large number of experiments. This observation was performed in the comfort zone at  $30^{\circ}\text{C}$ . The rectal temperature was constant in the basal hour. Heat production shown by the dotted line was the same as heat loss. In the short transition period and in the subse-

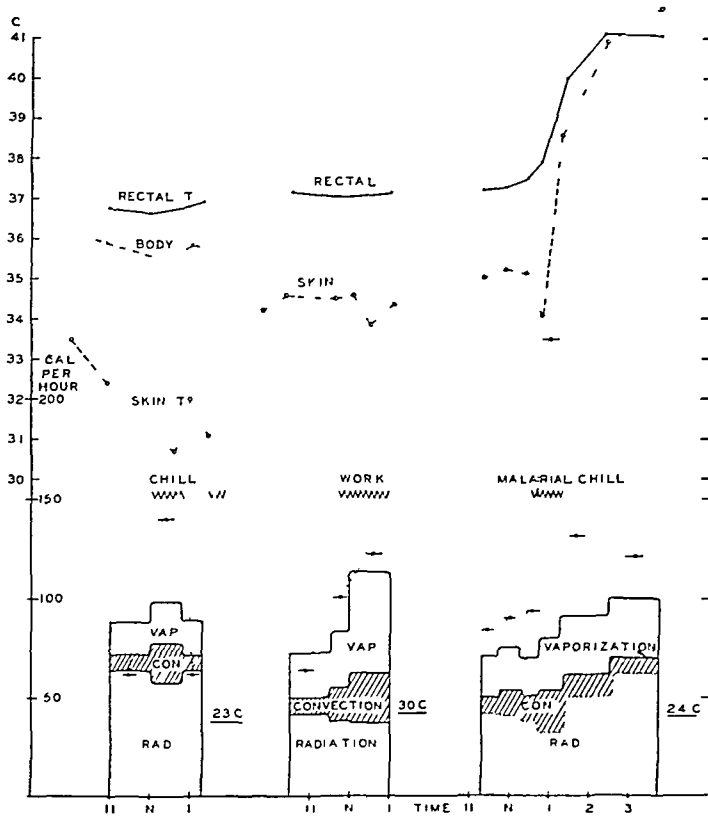


Fig 10—Chills and Muscular Exercise The first diagram shows chills which occurred spontaneously when the naked man was lying motionless in the calorimeter at a temperature of 23° C The dashed lines connected by dots show heat production, the columns heat loss

The second diagram shows the effect of moderate exercise at a temperature of 30° C

The third diagram represents a malarial chill studied in 1918 There were no direct determinations of skin temperature or radiation but estimations have been supplied from later experiments

quent longer period when moderate work was performed, heat production increased and heat loss kept pace so that the storage of heat in the body was scarcely affected. When work was started convection rose and in the third period there was a slight outbreak of sweat, increasing vaporization markedly. The rise in convection and vaporization cooled the skin so that radiation was decreased, proving once more that it was possible to lose more heat through a cool skin than through a warm skin. This experiment demonstrates nicely the delicate regulation of the tem-

perature but here it was an adjustment of heat loss through greater vaporization in order to balance the increasing heat production

The third diagram of Fig 10 is a recalculation of the often quoted case of George S studied by Barr and Du Bois<sup>16</sup> in the calorimeter in 1918 At that time we did not have a radiometer and the dashed line indicating changes in the skin temperature and the blocks for radiation are reconstructed from evidence that we have obtained on other patients with chills They are only approximate

George S came to Bellevue with a history of chills, recurring at regular intervals We placed him in the calorimeter about two hours before an expected chill and measured his heat production and heat loss In the first two periods his temperature was normal and heat production about 90 calories per hour, his heat loss a trifle lower In the third period with the onset of a violent chill which lasted thirty-five minutes, heat production rose to 250 calories per hour, heat loss was almost unchanged, and he stored 113 calories in his body with an abrupt rise in rectal temperature to about 40° C (104° F) After the subsidence of the chill his metabolism fell but did not quite reach his previous level He continued to store a little heat in the body After the calorimeter observations he began to sweat, heat loss exceeded production, and the body temperature fell to normal Judging from other chills, convection must have increased, surface temperature and radiation must have fallen We have observed in other chills a rise in skin temperature until in some patients it is even higher than the rectal temperature

Here the temperature regulation was very different from that observed in two other situations shown in this figure In all probability the disruption of the malarial parasites had caused a sudden change in the level to which the temperature regulating center was adjusted The center demanded a body temperature of 40-41° C and it found the body 4 degrees too cold Therefore it summoned its emergency mechanism, a chill, and in the course of an hour or two accomplished the desired result This, of course, was aided by the fact that the skin was kept relatively cold and heat loss maintained at or near a minimum Following the chill the regulatory center desired a return to the normal level of temperature and accomplished this by calling upon its emergency mechanism of sweating, aided to a slight extent by increasing radiation from an unusually warm skin Increased radiation, however, seldom adds more than 15 calories per hour

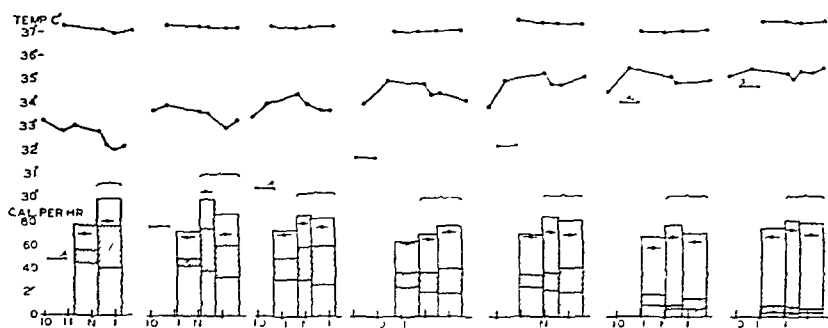


Fig 11—Experiments with an electric fan After one basal hour the large fan at the foot of the calorimeter was started Convection was increased greatly except in the experiment when the air was as warm as the skin

Passing from the chill experiments, the next factor to be considered is air movement. In a number of our experiments we started a large electric fan at the foot of the calorimeter shortly after the termination of the basal period. In Fig 11 the observations are arranged according to ascending temperatures between  $27.4^{\circ}$  and  $34.7^{\circ}$  C. The first column in each case shows the heat loss in the basal period. It will be noted that in the colder experiments the fan caused a rise in heat loss above the level of heat production. This resulted in a fall in skin temperature due chiefly to the increased convection. In the middle zone there was almost always a slight fall in skin temperature caused by the fan. In the warmest experiment at  $34.7^{\circ}$  C when the air temperature and skin temperature were practically the same there was no radiation, convection was unchanged, vaporization accounted for almost the entire heat loss, and the total dissipation of calories from the body was not affected. Skin temperature and rectal temperature remained level. The subject's notes made during the experiment stated that he felt a little less uncomfortable when the fan was blowing. What did the fan accomplish? It did nothing except make a buzzing noise which aroused pleasant expectations in the mind of the subject.

The factor of exercise deserves more attention. In some experiments in the colder zone moderate exercise was introduced immediately after the first basal hour. Just as in the case of chills this muscular activity warmed up the body. The surplus heat was retained until the depleted heat reservoir had been filled and then the excess was dissipated by various channels.

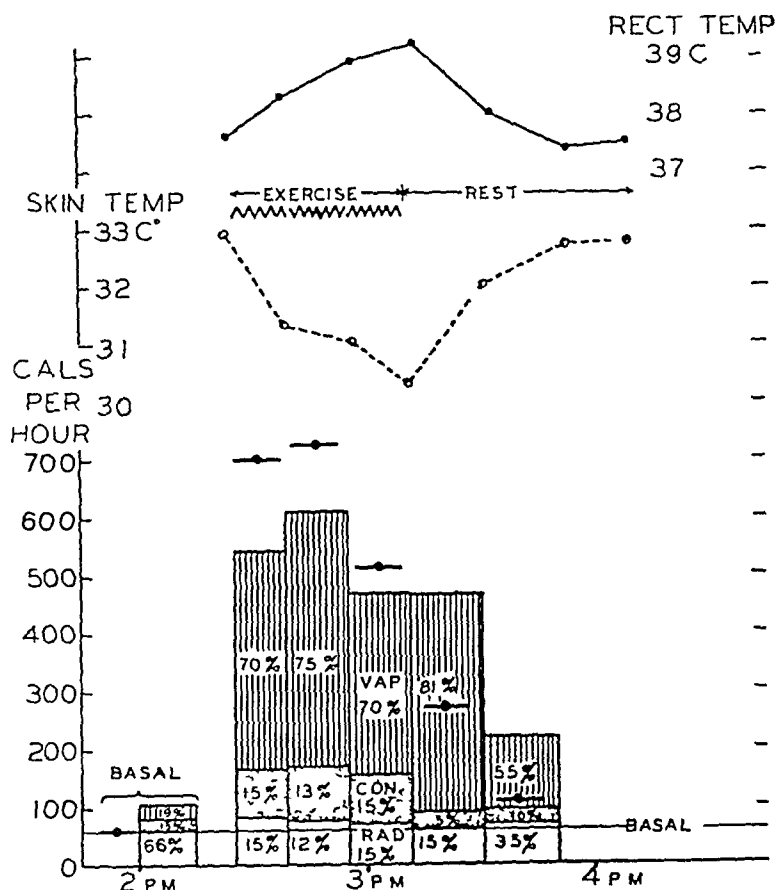


Fig 12—Diagram showing the effect of violent exercise. Normal control JDH played three games of squash racquets. The rectal temperature rose sharply to fever levels, the skin temperature fell. The round dots with horizontal lines through them show the estimated heat production, and the columns the estimated heat loss.

Our calorimeter is not large enough to measure more than mild activity but we were able to obtain outside the calorimeter fairly good estimates of heat loss during violent exercise. Two of the staff played three twelve-minute games of squash-racquets in a court at a temperature of 20° C. Radiation, skin temperature, and rectal temperature were measured every twelve minutes. Vaporization was estimated by weighing the man every twelve minutes and making allowance for the small amount of sweat that dripped from the body. Heat production could be calculated roughly from these factors. The results on one man are shown in Fig 12. The men were excellent players and they exerted themselves to the utmost. Heat production rose to the rate of 600-800 calories per hour but heat loss did not keep pace. The average skin temperature fell three

degrees and therefore radiation decreased. Convection rose markedly as the men rushed about the court. The great bulk of the burden fell on vaporization but even this was lagging under an excessive demand. The body did not lose heat fast enough and the rectal temperature rose three degrees.

As soon as the men stopped playing and rested in the dressing room heat loss was able to exceed heat production. Vaporization remained high, and in thirty-five minutes all the excess of heat had been dissipated. The skin temperature rose to its former level and the rectal temperature fell to normal. Soon after the game started the skins of the players had turned pink and it was evident that there was an increased flow of blood just beneath the surface. With a rectal temperature of  $39^{\circ}\text{C}$  and an average skin temperature of  $31^{\circ}\text{C}$ , there was a gradient of eight degrees between the moist surface of the body and the blood just beneath the epidermis. There must have been a tremendous interchange of heat in the zone one-half or 1 mm deep.

Until a few days ago we held the opinion that the rise in rectal temperature during exercise was due to the inability of the body to lose heat fast enough. A very recent publication by Marius Nielsen<sup>21</sup> of Krogh's laboratory forces us to change our views on this subject. In a series of beautiful experiments with a bicycle ergometer he has shown that the rectal temperature rises rapidly when work begins and then tends to flatten out at a level determined by the severity of the exercise. Drastic changes in the temperature and movement of the external air make little or no difference in the level to which the body adjusts itself. The fact that when this level is attained during severe work the men can lose heat as rapidly as it is produced proves that during the milder grades the body had not employed its utmost capacity in dissipating calories. Nielsen has shown that during work the temperature regulating center is adjusted at a higher level and maintains the body very nicely at this level.

We have not time to survey our limited number of experiments on the effects of clothing. Suffice it to say that we have found that ordinary clothing does not change the fundamental concepts regarding the proportions of heat lost by the various channels but clothing does extend the comfort zone far into the colder ranges. The matter has been thoroughly studied recently by Winslow, Herrington and Giggie.<sup>20</sup>

This detailed investigation of heat loss through the various channels has rather important bearings on the problems of heating and air con-

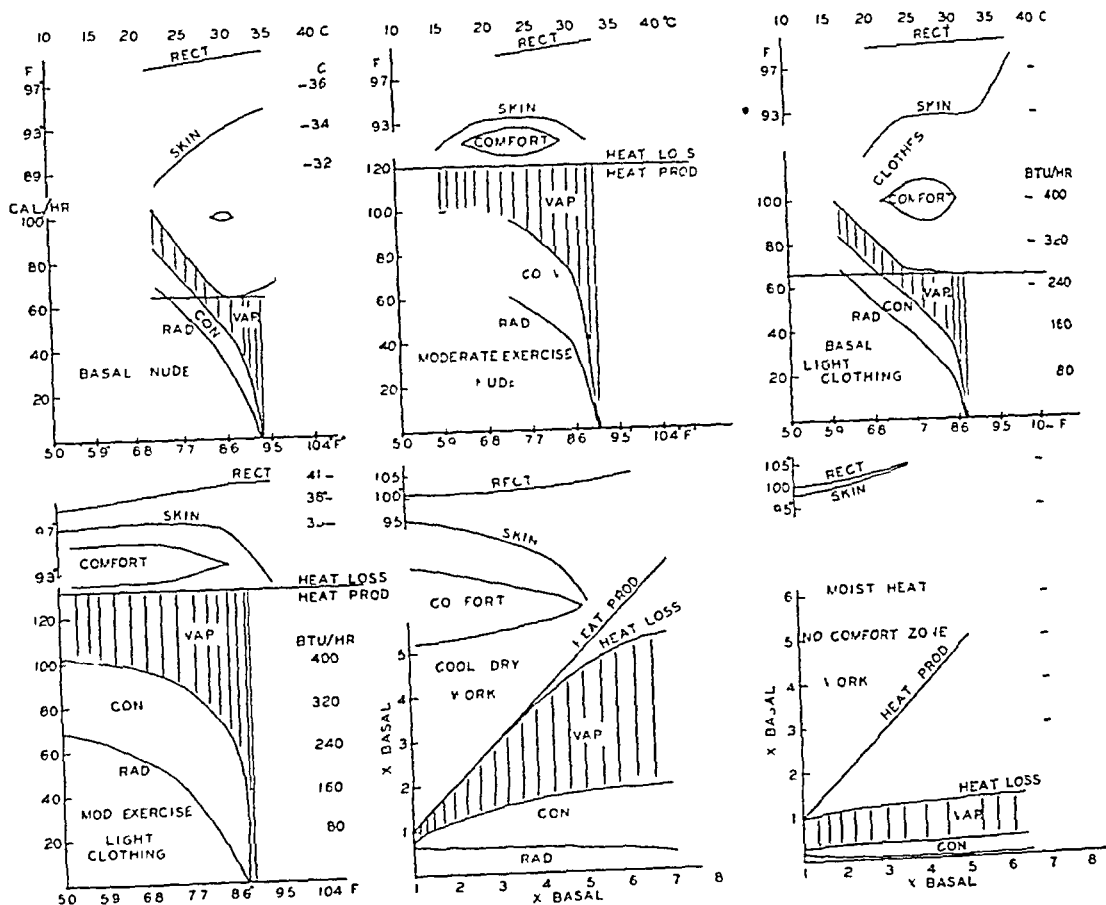


Fig 13  
COMFORT ZONES UNDER VARIOUS CONDITIONS

1 Basal nude Narrow comfort zone where heat loss and heat production are equal

2 Moderate exercise, nude Comfort zone wider and at a lower range

3 Basal with light clothing Comfort zone at a lower range than in the case of the nude man In the colder part of this zone the skin is warmer than the surface of the clothing, in the warmer part of the zone the skin is cooler than the clothing

4 Moderate exercise with light clothing Comfort zone extends far into the cold range

5 Work in a cool, dry atmosphere Abscis-

sae show heat production in terms of the basal metabolism, six times basal representing moderately severe exercise The ordinates show heat loss The comfort zone is wide

6 Work in a warm, very humid climate Vaporization is impaired to such an extent that heat is retained in the body There is no comfort zone

[1 and 2 are based on an adequate number of calorimeter experiments, 3 and 4 on a few observations of our own, and 5 and 6 are taken from the work of other observers]

ditioning of rooms In order to outline some of these problems to serve as a basis of further studies we have sketched out various conditions in Fig 13 The first two diagrams are based on a considerable number of

experiments, the second two with clothing on relatively few subjects, and the last two are largely theoretical, based on the work of other observers. The first diagram sketches the conditions shown in Fig. 9 based on the study of the two naked men in air temperatures from 70 to 94° F. There was a small comfort zone where heat loss equalled heat production. The second figure shows the conditions when the naked men were exercising in the calorimeter. Heat loss and heat production equalled each other over a wider range at a lower temperature, and the comfort zone was much more extensive. The third chart shows the conditions when the men were lightly dressed. The surface temperature of the clothes was roughly proportional to but distinctly above the level of the air while the skin temperature was warmer than the surface of the clothes in the cold zone, cooler in the hot zone when the man was sweating. The region of comfort as we all know was much more extensive than in the case of the naked man. The fourth diagram shows the combination of light clothing and moderate exercise with a comfort zone extending far into the cold region, depending on the extent of clothing and degree of exercise.

The last two diagrams on this chart are gathered from studies in the literature with extrapolations from our own work. In them the abscissae show the extent of work expressed in terms of the basal metabolism, six times basal representing fairly severe exercise. The ordinates show heat loss in terms of basal metabolism. When a man works in cool, dry air, the rectal temperature rises depending on the severity of the work, the skin becomes cooler, heat loss eventually becomes equal to heat production, the comfort zone is wide until the exercise is excessive. When, however, work is performed in a hot, moist atmosphere, the vaporization is no longer able to dissipate more than a small amount of heat from the surface of the body. Heat loss lags farther and farther behind heat production with increased amounts of work. Rectal and skin temperatures rise rapidly. The comfort zone is conspicuous by its absence.

Time does not permit the discussion of the temperature regulating center in the hypothalamus. It seems to be controlled by two factors, the temperature of the blood reaching the brain and the changes in the temperature of the skin. The pathways for the sensory connections from the skin through the spinal cord to the brain and then back from the brain to the skin, muscles, and internal organs are fairly well known. The internal mechanism of the small group of cells constituting the regulating center



remains a fascinating mystery

This review of the subject of temperature regulation and heat loss is necessarily incomplete, but Gajda<sup>22</sup> has recently published an excellent survey. The field of study has been particularly active during the last few years and the advances have been great, chiefly on account of the fact that well trained biophysicists have been induced to participate in these studies. How far the modern investigations will take us is difficult to estimate. We shall undoubtedly learn more about the thermo-regulating mechanism, we shall learn more about the blood flow of the skin and its nervous control, and the clinical applications of this will probably be numerous, we shall get a better insight into the mechanism of fever and heat regulation during muscular exercise. We shall have a much better approach to the problem of comparing the basal metabolism of various species of animals. We shall learn more about artificial fevers and also obtain information that will help our friends, the air-conditioning engineers. It is doubtful if any of this work will have the slightest influence on clothing. In this field custom and fashion reign supreme.

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## THE MEDICAL-SURGICAL SPLENOPATHIES\*

*Introduction*

ALLEN O WHIPPLE

SOME TEN years ago a group of internists, pathologists and surgeons agreed to pool their interests in diseases of the spleen and hematopoietic system and the Combined Spleen Clinic, as it is now called, was started at the Columbia Medical Center. The advantages of seeing patients with such disorders before, during and after the therapy had been agreed to, whether medical, surgical or roentgenological, soon became apparent, and may be summed up under three headings:

- 1 Advantages to the patients are definite in having a more active concentrated study of their lesions, a more accurate diagnosis, a therapy agreed upon by the group, and lastly a follow-up by the same group to determine the late results as a basis for advice to future patients.
- 2 Advantages to the members of the Clinic, as clinicians and teachers, are evident in the study of an increasing number of patients and in clarifying their ideas in diagnosis, pathology, therapy and prognosis.
- 3 The stimulus to clinical and experimental investigation of problems arising in the diagnosis and treatment of patients seen in the Clinic is obvious.

During the past ten years we have seen 1,457 patients with the lesions as classified in Table I. It is obvious that many of these blood and spleen dyscrasias are strictly medical in their therapy, others roentgenological, others surgical, and a fairly definite group where therapy is difficult to advise. The leukemias and primary anemias are studied and cared for on the medical services by Doctors McAlpin and West. The splenomegalies, of known and undetermined etiology, are studied by the combined group.

The organization of the Clinic is of importance and is graphically

\* From the Department of Surgery, Columbia University College of Physicians and Surgeons and the Spleen Clinic of the Presbyterian Hospital, New York City.  
Delivered November 4, 1938 in the Eleventh Annual Graduate Fortnight.

TABLE I  
NUMBER OF CASES TO OCTOBER, 1938

Type	Cases	
Hemolytic Jaundice (typical)	43	30 with splenectomy 13 without "
Hemolytic Jaundice (atypical)	15	7 with " 8 without "
Normal Splenectomy	30	
Splenomegaly of Undetermined Origin	47	43 with " 4 without "
Banti's Syndrome		
(1) Cirrhosis	64	22 with " 42 without "
(2) Schistosomiasis	11	11 with "
(3) Outside Pressure on Splenic Vein	3	
(4) Splenic Vein Thrombosis	8	3 with " 5 without "
(5) Cavernomatous Transformation of Portal Vein	2	2 with "
(6) Stenosis of Portal Vein	1	1 with "
(7) Obstructive Factor Undetermined	33	22 with " 11 without "
Idio-thrombocytopenic Purpura	42	22 with " 20 without "
Miscellaneous Purpura	49	11 with " 38 without "
Aplastic Anemia	54	
Pernicious Anemia	231	
Secondary Anemia	84	
Sickle Cell Anemia	10	
Miscellaneous Anemias	88	
Eosinophilia	13	
Hemophilia	15	
Infectious Mononucleosis	71	
Acute Leukemia	79	
Chronic Myeloid Leukemia	98	
Chronic Lymphatic Leukemia	89	
Hodgkin's Disease	141	
Neoplasm	70	
Polycythemia	66	

presented in Chart I. It is to be emphasized that the general practitioner and family physician is the beginning and end of this scheme. It is he who, as a rule, is first consulted and sends the patient for opinion and consultation and it is to him that we try to return the patient and whose co-operation we seek in having the patient return for follow-up studies.

The second feature of this organization that we wish to bring to your attention is the central and essential laboratory for the hematological studies of these patients. Before, during and after the therapy used in the individual case, the blood counts and various blood studies should be done by the same group of carefully trained and experienced hematologists. Unless this is done, the records in the Clinic and the conclusions drawn from the study of the patients will be thoroughly unreliable.

# ORGANIZATION SPLEEN CLINIC

## COLUMBIA-PRESBYTERIAN MEDICAL CENTER NYC

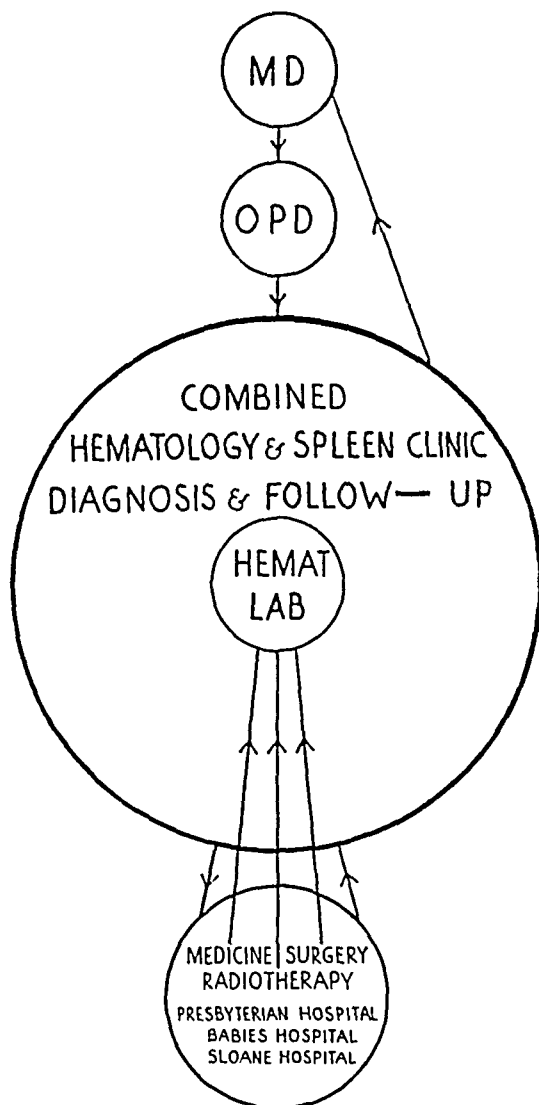


Chart 1

It is the desire of the members of this Clinic to pay tribute to the accurate work and interested co-operation of Miss Katherine Edsall, Miss Mary Whipple, Miss Catherine Illyne and Miss Hazel Maxwell, who have carried on the work in this laboratory

In conclusion I should like to emphasize that combined clinics in diseases of systems requiring various types of therapy give the best results from the standpoint of therapy, teaching and research

## HEMOLYTIC JAUNDICE

*Its Diagnosis, Behavior and Treatment\**

W P THOMPSON

T

WO AND a half years ago we presented here a paper of this same title<sup>1</sup> Tonight we are to repeat much of what was said then, but in the light of considerable further experience

Our methods of study remain unaltered Our patients continue to be followed at regular intervals by the combined Medical and Surgical Spleen Clinic group Laboratory procedures continue to be done by the Spleen Clinic technicians and our central files expand rapidly

The term "hemolytic jaundice" is still used for the general diagnosis of all patients presenting jaundice and anemia due to increased red blood cell destruction There is, in addition, almost always an associated splenomegaly and an increase in the number of reticulocytes in the peripheral blood

The term "hemolytic jaundice" is still being divided into two clinical subdivisions The first of these is a uniform, recognizable, curable entity This disease, formerly known as congenital hemolytic jaundice, is now known, at the suggestion of Dr E B Krumbhaar<sup>2</sup>, as spherocytic jaundice, a term which is far more accurate The second subdivision consists of a heterogeneous variety of disturbances grouped together under the intentionally vague term—atypical hemolytic anemia

## SPHEROCYTIC JAUNDICE

Spherocytic jaundice is in our experience a uniform and readily recognizable disease entity provided certain diagnostic criteria are rigidly maintained It is a chronic disease of long duration and of relative mildness Acute exacerbations may occur but these episodes are not common The presenting symptom is chronic variable jaundice and

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.  
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TABLE I

## TYPICAL HEMOLYTIC INDICES - NONSPONTANEOUS\*

Case	Age	FIRST BLOOD COUNT							Duration of Illness, Years	Spleen	Results As of October 1918
		Date	Hemo- globin Per Cent	Rcd Blood Cells Millions	White Blood Cells	Neutro- phils Per Cent	Reticu- locytes Per Cent	Irradi- ability			
1	56	2/26/22	35	2.8	15,000	77	Increased	0.55	0.5	6 cm below costal margin	Died 6/3/22, cause unknown
2	8 mo	3/2/28	26	2.4	35,400	22	10.0	0.60	0.6	8 cm below costal margin	Left against advice
3	50	11/15/29	68	3.2	5,300	59	15.5	0.525	30	Enlarged	Symptoms continue, 39 yrs
4	25	6/8/31	41	3.1	6,700	70	24.0	0.675	20	26 cm below costal margin	Symptoms continue, 27 yrs
5	18	7/14/31	78	4.1	9,000	66	10.6	0.575	17	2 cm below costal margin	Symptoms continue, 24 yrs
6	14	8/2/33	55	2.7	6,400	68	12.1	0.625	5	1 cm below costal margin	Symptoms continue, 9 yrs
7	57	7/3/35	57	3.4	5,000	40	10.9	0.625	25	10 umbilicus	Symptoms continue, 23 yrs
8	7	9/25/35	68	4.1	13,200	61	17.8	0.65	1	To umbilicus	Symptoms continue, 7 yrs
9	7	9/25/35	74	3.6	12,200	43	13.6	0.65	1	7 cm below costal margin	Symptoms continue, 7 yrs
10	9	9/25/35	60	3.3	7,900	51	11.5	0.65	5	8 cm below costal margin	Symptoms continue, 8 yrs
11	29	9/18/35	85	4.0	8,400	77	12.0	0.65	9	9.5 cm below costal margin	Symptoms continue, 11 yrs
12	37	6/17/36	90	3.8	6,900	58	19.8	0.60	37	8 cm below costal margin	Symptoms continue, 39 yrs
13	30	5/10/38	76	3.2	12,500	59	23.6	0.65	30	9 cm below costal margin	Symptoms continue, 30 yrs

\*All patients had anemia and were jaundiced

the outstanding physical finding is splenomegaly. The positive diagnosis is made in the laboratory. In all cases of spherocytic jaundice, the peripheral blood contains the spherical red cells that we believe are as pathognomonic of this disease as are the sickle cells of sickle cell anemia.

The Spleen Clinic has now had the opportunity of studying forty-three cases of this typical disease. Of these forty-three, thirty have had their spleens removed. The more important clinical and laboratory data are presented in the accompanying Tables I and II.

#### ATYPICAL HEMOLYTIC ANEMIAS

In marked contrast to spherocytic jaundice is our experience with the atypical hemolytic anemias. In the former group a definite diagnosis is readily available, a prognosis as to the behavior of the disease may be made with considerable assurance, and the results of splenectomy can be predicted with security.

The atypical group comprises a total of fifteen cases presenting chronic acholuric jaundice, anemia with evidence of regeneration, and splenomegaly. In all of this group the possibility of spherocytic jaundice had to be considered but in all of these, diagnosis of spherocytic jaundice could not be sustained because the blood failed to show the spherical cells with their attendant fragility changes.

Although the total number of patients included in this group is only slightly more than we reported two and a half years previously, our experience has increased enormously. We have now had the opportunity of studying three separate family groups in which hemolytic anemia and jaundice were present in various generations and in which the diagnosis of spherocytic jaundice might well have been made, except for the absence of spherocytes. And it is our present conception that a familial type of hemolytic anemia does occur, that is not spherocytic jaundice that is not sickle cell anemia and that is not the erythroblastic anemia described by Cooley. What the nature of this disturbance may be we do not know, but we do know, after having removed several spleens that splenectomy in no way alters the disease process and the splenic histology is not that so characteristic of the spherocytic type.

During the past two and a half years there have been several examples of a subacute to acute hemolytic anemia with jaundice seen in association with sulfanilamide medication as well as several instances of the disturbance described by Lederer.



TABLE II

## TYPICAL, HEMOLYTIC JAUNDICE—SPLENECTOMY\*

Case	Age	Date	Hemo- globin Per Cent	Red Blood Cells Millions	White Blood Cells	Neutro- phils Per Cent	Reticu- locytes Per Cent	Irregu- larity	Micro- cytes Per Cent	Dura- tion of Jaun- dice	Splenec- tomy	Spleen	Pathology of Spleen	Pathology of Gall bladder	Dura- tion of Follow Up	Results of Oper ation
14	18	6/21/05	70	3 5	4,500	48	1 1	0 475	Many 13	15 yrs	1/10/20	Enlarged	Typical	Stones	18 1/2 yrs	Excellent
First blood count		3/16/36	104	5 0												
15	14	7/11/12	50	2 7	10,000	45	2 6	0 5+	Present 11	18 yrs	8/11/22	720 Gm	Typical	No stones	16 yrs	Excellent
First blood count		6/ 2/37	100	5 3	14,500	51	6 0	0 60		2 yrs	9/28/25	Enlarged	Typical	?	6 yrs	Died August 1931, of poliomyelitis
16	4	11/23/23	70	4 3	13,400	63	6 0	0 52		5 yrs	6/ 1/26	1 032 Gm	Typical	Stones	Died 3 days postoperative	
First blood count		12/12/29	80	5 2			0 55			15 yrs	11/ 8/29	675 Gm	Typical	No stones	8 1/2 yrs	Excellent
17	35	6/ 2/26	70	3 7	5,400	66				6 yrs	6/23/25	175 Gm	Typical	No stones	13 yrs	Excellent
First blood count										1 yr	?/ ?/30			?	?	Record incomplete
18	28	11/ 3/29	60	5 1	7,300	63	0 9	0 425	Present	11 yrs	10/23/30	970 Gm	Typical	No stones	3 5 yrs	Died November 1931, Carcinoma of rectum
First blood count										5 yrs	6/15/31	1,460 Gm	Typical	Stones	7 yrs	Excellent
19	25	9/ 8/24	75	3 8	8,100	74	15 0	0 58	Present 12	19 yrs	?/ ?/29			?	3 yrs	Excellent
First blood count		4/15/36	94	5 1			2 7	0 525		15 yrs	3/ 1/32	1,135 Gm	Typical	No stones	1 yr	Died 3/5/33, Multiple sarcomatosis
20	8	8/ 4/30	65	3 0	8,000	72	9 1	0 525	Present	8 mos	2/ 2/33	265 Gm	Typical	No stones	5 yrs	Excellent
First blood count										5 yrs	1/ ?/27	Enlarged		?	7 yrs	Excellent
21	45	10/14/30	55	3 6	10,000	78	3 0	0 60	Present	9 days	3/19/31	750 Gm	Typical	No stones	1 yr	Excellent
First blood count		2/21/34	85	3 6			1 3	0 575		10 yrs	5/25/31	1,000 Gm	Typical	No stones	1 yrs	Excellent
22	26	4/23/31	42	2 4	8,900	67	15 1	0 575	Many 11							
First blood count		5/ 6/36	109	4 9			2 7	0 525								
23	20	3/10/32	98	4 9			0 6	0 575	Present							
First blood count																
24	59	2/14/32	40	1 7	7,400	72	15 7	0 55	20	15 yrs	3/ 1/32	1,135 Gm	Typical	No stones	1 yr	Died 3/5/33, Multiple sarcomatosis
First blood count		6/ 8/32	82	4 7			1 0	0 525	18	8 mos	2/ 2/33	265 Gm	Typical	No stones	5 yrs	Excellent
25	28	1/13/33	52	2 5	11,000	67	33 6	0 625	17	5 yrs	1/ ?/27	Enlarged		?	7 yrs	Excellent
First blood count		5/ 5/34		4 4					17	9 days	3/19/31	750 Gm	Typical	No stones	1 yr	Excellent
26	48	?/ ?/25	35	5 3			2 7	0 50	Present 8	10 yrs	5/25/31	1,000 Gm	Typical	No stones	1 yrs	Excellent
First blood count		3/21/34	96				78 6	0 625	21							
27	30	3/ 1/34	45	1 5	21,300	76	8 7	60	Present 9							
First blood count		3/ 2/38	96	5 1	16,500	60										
28	35	4/12/37	90	4 7	16,100	56	2 5									
First blood count																

\*All patients had anemia and were jaundiced

TABLE II (Continued)

[illegible]

TABLE III

## ATYPICAL HEMOLYTIC ANEMIA\*

Case	Age	FIRST BLOOD COUNT								Duration of Symptoms	Splenectomy	Spleen	Pathology of Spleen	Pathology of Gallbladder	Duration of Follow Up	Remarks
		Date	Hemoglobin Per Cent	Red Blood Cells Millions	White Blood Cells	Neutrophils Per Cent	Reticulocytes Per Cent	Fragility	Microcytic Per Cent							
44	21	3/1/20	50	4.7	6,700	62	1.0	0.55	0	<i>Cases in which splenectomy was performed</i>						
45	27	7/31/29	20	0.91	31,200	80	19.0	0.425	0	1 1/2 yrs 12/6/24	397 Gm	Normal	No stones	1 1/2 yrs	Improved diagnosis unknown	
46	63	9/19/31	35	1.3	3,300	78	37.6	0.125	0	4 days 10/25/29	510 Gm	Marked blood formation	Stones	1 yr	acute course partly arrested, diagnosis unknown	
47	16	6/23/33	80	3.9	10,000	59	5.7	0.125	0	1 wk 10/31/31	680 Gm	Marked blood formation	No stones	1 mo	Died 12/5/31, autopsy, splenectomy no help, diagnosis unknown	
48	1 1/2	9/16/33	38	1.6	4,300	39	13.2	475	0	11 yrs 6/28/35	510 Gm	Not typical	No stones	3 yrs	Situation 3 yrs post-op unchanged	
49	2 mo	2/4/37	39	1.7	7,700	32	2.6	525	0	9/21/33	225 Gm	Normal	Normal	5 yrs	Slightly improved	
50	21	8/3/37	82	3.3	7,800	74	39.0	15	0	1/16/38	225 Gm	Normal	Normal	5 mos	Slightly improved	
51	44	8/4/28	15	0.61	10,400	74	25.0		0	8/21/37	370 Gm	Sclerosis	Pigment stone	None	Died, Post-op shock	
52	56	9/20/29	35	1.5	7,700	88	6.4	0.425	0	<i>Cases in which splenectomy was not performed</i>						
53	72	1/15/32	48	1.8	6,500	76	27.2	0.425	0	6 mos	580 Gm	Sarcoma	Sarcoma		Died 8/6/28, autopsy, sarcoma of spleen	
54	52	8/4/30	33	1.3	2,300	73		Normal	0	None	1,300 Gm	Sarcoma	Normal		Died 10/23/29, autopsy, sarcoma of spleen	
55	64	3/3/32	64	3.1	3,200	44	10.2	0.45	0	None	820 Gm	Sarcoma	Sarcoma		Died 5/23/35, autopsy, radiotherapy helped for time, sarcoma of spleen	
56	21	4/5/33	108	6.1	15,700	74	4.6	0.50	0	None	Pulpable			1 1/2 yrs	Died—Syphilis of spleen	
57	80	11/30/36	32	1.4	25,000	88	39.5	Normal	0	None	3 cm below costal margin 310 Gm		Sarcoma	2 mos	Died 7/5/32, apparently cerebral accident, diagnosis unknown	
58	60	4/13/37	58	1.9	5,300	60	20.3	Normal	0	None				3 yrs	No change 1/8/35, diagnosis unknown	
										1 1/2 yrs					Died—Retic Cell sarcoma	
															Condition unchanged	

\* All patients had anemia (except patient 56) and all were jaundiced

Otherwise, our group of atypical hemolytic anemias remains as previously reported. Details of this group are available in the accompanying Table III.

### THE NATURE OF SPHEROCYTIC JAUNDICE

The clinical study of patients with spherocytic jaundice, before, during and after operation, has led to certain conclusions concerning its behavior. The symptoms of chronic anemia with jaundice may appear at any age or an enlarged spleen may be found in an individual being examined for some unrelated complaint. The anemia may be mild or severe, or, in the latent cases, the blood count may be quite normal. The degree of jaundice varies likewise but is always proportional to the degree of anemia. The percentage of reticulocytes also varies within wide limits, depending again on the severity of the hemolytic process.

In every case of spherocytic jaundice the peripheral blood smear contains erythrocytes the diameter of which is obviously much less than normal but which in addition show no central pallor. In wet preparations these small cells appear spherical. With the micromanipulator these cells can be slowly and carefully examined and their spherical shape confirmed.

It is important that these cells should be detected and counted in wet film preparations with, when possible, the aid of the micromanipulator. Techniques that give the mean corpuscular volume may be misleading, as these spherical cells form only a small proportion of the total red cell colony, and many of the remaining cells, the reticulocytes, may be considerably larger than normal. In the presence of a high degree of reticulocytosis, mean corpuscular volume readings may be on the high side of normal and the spherical cells remain undetected.

It was not until the recent work of Haden<sup>4</sup> appeared that the relationship between shape, size and hemolysis was conclusively proved. His work leaves no doubt about the fact that these spherical cells are alone responsible for the fragility changes seen in all cases of spherocytic jaundice.

In addition, evidence is available to suggest a serious consideration of the importance of these spherical cells in the production of the active disease process.

This chain of evidence, although fragmentary in places, may be presented in order.

1 The fact may be accepted that all patients with spherocytic jaundice, as well as their relatives with the latent disease, have these spherical microcytes circulating in the peripheral blood. These abnormal cells constitute from 10 to 25 per cent of the total number of erythrocytes, the remaining cells being either reticulocytes or normal red cells. We have never observed reticulation in the spherical cells.

2 These spherical cells are directly responsible for the fragility changes to hypotonic salt solution.

3 These spherical cells appear to be selectively removed from the general circulation of the spleen, where they are found in larger numbers than in the peripheral blood.

4 There is enough evidence, I believe, to warrant the assumption that all the increased red blood cell destruction that results in the active phase of the disease takes place within the spleen. Some of this evidence is direct, most of it is inferred.

Direct evidence can be procured only by measuring the serum bilirubin concentrations in the blood of the splenic artery and vein at the time of operation. Obvious technical difficulties interfere with the collection of the necessary specimens. In spite of these difficulties we have found that the blood of the splenic vein contains more pigment than does the blood of the splenic artery.

These observations are in accord with the figures obtained by Rich and Rienhoff<sup>5</sup> in an active case of hemolytic jaundice and show that the spleen is actively destroying erythrocytes.

Indirect evidence concerning the activity of the spleen in this disease may be procured by observing the effects of splenectomy. Our therapeutic results in the thirty cases in which splenectomy was performed are uniform and coincide with the results of others. Removal of the spleen is immediately followed by cessation of the increased hemolytic activity. Relief is immediate and, apparently, permanent.

A study of the factors that might be influenced by splenectomy, results in the acceptance of only one, the excessive hemolysis stops. I can see no reason to consider any other influence, as the cessation of excessive hemolysis will explain all the changes observed.

With the removal of the site of increased destruction of erythrocytes, the serum bilirubin and the urobilin excretion figures drop promptly to normal levels. The already overactive bone marrow rapidly raises the erythrocyte concentration in the peripheral blood. As the red blood cell

count rises, the stimulus for new erythrocytes falls and the proportion of reticulocytes drops. All these changes toward normal appear within a few hours after operation and are concluded in from two to three weeks. The results of the operation appear to be permanent.

Only one patient has failed to show these clear cut results. This patient, a young woman, was admitted with spherocytic jaundice of relatively brief duration, of considerable intensity. The history, physical findings and laboratory data were all complete and unquestioned. In July of this year, her spleen was removed and the spleen sections were typical in all respects. Following splenectomy the disease process appeared to subside for the first few days but then reappeared with renewed vigor. During the next three months spherocytic jaundice in its active phase continued in spite of multiple transfusions; the anemia increased and the reticulocyte level rose to above 75 per cent. A report of a similar instance appeared during the summer from England.<sup>6</sup> In the British case, the second exploratory laparotomy, done with the hope of finding an accessory spleen, revealed an ovarian tumor which was subsequently found to be a teratoma. Removal of this tumor was immediately followed by cessation of the hemolytic activity and a subsidence of all symptoms. We were unable, in our patient, to find any abnormalities on pelvic examination and the Aschheim-Zondek test was negative. Finally, it was decided that additional spleens must be present and that a second operation had to be performed. Two days after this decision was reached, an acute hemolytic crisis set in, the patient's red count fell rapidly to 600,000, the reticulocytes rose to 90 per cent and the patient died of acute spherocytic jaundice. At autopsy the left upper quadrant contained many accessory spleens, varying in size from 1 cm. to 6-8 cm. in diameter and these accessory spleens presented the typical histology of this disease process. Our one failure, then, seems to have been a result of a congenital abnormality.

The only other theoretically possible effect of splenectomy would be some change in the spherical cells and their fragility. That some such change does occur has been suggested at various times by various authors. Their conclusions are as a rule variable and the changes usually observed are slight shifts in the fragility test.

Our observations warrant the definite conclusions in the post-splenectomy cases that the spherical cells persist with their attendant fragility changes for as long after splenectomy as time has permitted.

observation The proportion of these typical cells may vary within relatively narrow limits but they have been demonstrated in patients sixteen years after operation in concentrations as high as 14 per cent

The recent report of Lord Dawson of Penn<sup>r</sup> of typical fragility changes persisting forty-five years after splenectomy leaves little doubt that the spherical cells are not affected by this surgical procedure

This evidence, I feel, warrants the conclusions that, given the inherited spherical microcytes and increased hemolytic activity, one has the condition known as spherocytic jaundice, and that this disease, once active, remains active until the site of increased hemolytic activity is removed

Three important questions still remain unsolved

- 1 Little or nothing is known about the genetics of transmission of these spherical cells

- 2 Little or nothing is known about the factors that initiate the excessive hemolysis which signals the onset of the active disease It is known that individuals exist, as members of spherocytic families, whose blood contains these spherical cells and in whom increased hemolysis is not taking place We also know that these latent cases may become active at any time in their career from, in our series, the age of six weeks to the age of fifty-eight years We also know that when the disease once becomes active, spontaneous remission will not occur and that chronic anemia with jaundice will persist until splenectomy But we have not been able to associate the change from latency to activity with any as yet discernible event Occasionally an acute infection precedes the onset of jaundice, in the majority of cases no such history can be elicited

- 3 We do not know whether a normal spleen interposed in a circulation containing spherical erythrocytes would behave as and assume the histologic characteristics of a spleen presenting spherocytic jaundice

### CONCLUSIONS

- 1 Hemolytic anemia with jaundice and splenomegaly has been observed in fifty-five patients

- 2 This syndrome may be separated into two groups

- (a) Spherocytic jaundice

- (b) Atypical hemolytic anemia

- 3 Spherocytic jaundice is a clear cut, definite disease entity the course of which can be predicted and the mechanism of which is begin-

ning to be understood

4 The atypical hemolytic anemias comprise a heterogeneous group of conditions in which there is increased red cell destruction

5 The symptoms of spherocytic jaundice are promptly, completely, and permanently relieved by splenectomy The atypical hemolytic anemias have not been benefited by this procedure

6 Accurate preoperative diagnosis is one of great importance and a familial incidence is of no differential value

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## CONGESTIVE SPLENOMEGALY\*

(BANTI'S SYNDROME)

LOUIS M ROUSSELOT

Two years ago a report<sup>1</sup> was presented from the Spleen Clinic of the Presbyterian Hospital outlining the results of splenectomy in Banti's syndrome. At that time we stressed the role of venous congestion or portal stasis in the production of the syndrome.

In this paper we wish to re-emphasize the same hypothesis and present additional evidence to support our contention that Banti's syndrome is not a primary splenomegaly, but rather a splenomegaly secondary to portal stasis. We have come to consider this group of splenomegalies under the general caption of "Congestive Splenomegaly," as this we feel more aptly describes the condition. The term "Congestive Splenomegaly" implies a primary congestive mechanism in the portal bed producing back pressure (splenic or portal vein hypertension). The venous stasis we believe subsequently produces a splenomegaly and certain other characteristic clinical and laboratory findings. This hypothesis is, of course, a reversal of Banti's<sup>2,3</sup> original idea that the disease began as a primary splenomegaly of toxic origin and later developed into cirrhosis of the liver. The conception of Banti's syndrome as a congestive splenomegaly and not a primary splenomegaly is not a new one. Warthin<sup>4</sup>, Eppinger<sup>5</sup>, and Larrabee<sup>6</sup>, all considered the possibility of portal congestion producing the Banti picture. Eppinger, in fact, frequently refers to the "Stauungsmilz" in his treatise on hepatolienal fibrosis.

McMichael<sup>7</sup> first suggested the term "Portal Hypertension." Both he and McNee<sup>8</sup> agreed that the factor of increased portal pressure plus the entry of toxic substances into the portal circulation probably accounted for the development of Banti's disease. McMichael likewise intimated that a condition of portal hypertension can occur in the absence of such gross changes as are found in a hobnail liver. This latter

\* From the Department of Surgery, Columbia University College of Physicians and Surgeons and the Spleen Clinic of the Presbyterian Hospital. Delivered November 4, 1938 in the Eleventh Annual Graduate Fortnight.

statement is significant, for we have been able to demonstrate conclusively portal hypertension in many cases without cirrhosis. Portal hypertension we believe is usually secondary to one of a variety of totally unrelated diseases. Any of these conditions is capable of initiating chronic portal obstruction. Our own experience as to the types of different primary lesions which may produce congestive splenomegaly will be discussed in due course. The distended and tense venous radicals in the splenic pedicle, and the rich venous collateral often enveloping the spleen, are visible phenomena that never fail to attract anyone familiar with surgery of the spleen in congestive splenomegaly. This local vascular condition occurs regardless of the nature of the obstructive factor in any particular case. Believing that portal hypertension may be a common factor associated with a variety of disturbances producing congestive splenomegaly, members of our Clinic<sup>9</sup> recently have made observations on the splenic vein pressures at operation. These studies are being continued. The determinations are made at the time of operation, after mobilization of the spleen, by inserting the needle of a venous pressure apparatus into the splenic vein. Simultaneously a reading is taken of the peripheral venous pressure in one of the veins of the arm.

Splenic vein pressure readings have now been made in fourteen cases of congestive splenomegaly or Banti's syndrome, and in fifteen controls having splenic lesions of other types. In the accompanying table these figures are listed in the various sub-groupings under which we now classify our various cases.

An obstructive factor as a cause for the portal hypertension was present in 52 per cent of our early cases and no such factor was ascertainable in 48 per cent of the same group. We have found that the 48 per cent group with no obvious obstructive factor comprises chiefly the portal bed and a liver biopsy were not part of the operative our oldest cases, treated at a time when a systematic exploration of routine. However, in the past two years we have done splenectomies on twenty-four patients in addition to the previously reported thirty-one cases. With more careful inspection of the portal bed and liver biopsy on all the recent cases and the securing of a post-mortem examination on several of the long-term cases in which an obstructive factor had previously been unknown to us the percentage of "unknowns" is now diminishing. In these last twenty-four cases therefore seventeen or

TABLE I

## VENOUS PRESSURES IN MILLIMETERS OF NORMAL SALINE

## BANTI—LAENNEC CIRRHOSIS

	<i>Splenic Vein</i>	<i>Arm Vein</i>
CM 1	225	12
GM 2	325	85
DP 3	150	125
NA 4	470	145
RB 5	370	30

## BANTI—SCHISTOSOMIASIS MANSONI

	<i>Splenic Vein</i>	<i>Arm Vein</i>
PR 1	230	50
AE 2	335	105
GP 3	500+	70
CC 4	415	125
LM 5	375	60

## BANTI—THROMBOSIS OF SPLENIC VEIN

	<i>Splenic Vein</i>	<i>Arm Vein</i>
JS 1	390	170

## BANTI—OBSTRUCTIVE FACTOR UNDETERMINED

	<i>Splenic Vein</i>	<i>Arm Vein</i>
LD 1	275	105 (p adrenalin)
GK 2	370	50
BS 3	330	55

## CONTROLS

	<i>Splenic Vein</i>	<i>Arm Vein</i>	<i>Diagnosis</i>
FH 1	190	65	Lymphosarcoma
RB 2	105	80	Hemolytic Jaundice
LL 3	220	205	Atyp Hemol Jaundice
NB 4	125	130	Hemolytic Jaundice
SS 5	215	40	Gaucher's
LL 6	190	107	Splen Undet Origin
WU 7	120	95	Hemolytic Jaundice
SJ 8	360	5 (severe shock)	Purpura
ZG 9	185	75 (beginning shock)	Pancreatic Adenoma
SL 10	190	210	Purpura
GC 11	235	165	Splen Undet Origin
EN 12	275	205	Atyp Hemol Jaundice
TK 13	70	300 (10 min later)	Purpura
MM 14	140	65	Purpura
JK 15	245	240	Lymphatic Leukemia

70 per cent have had a definite obstructive factor

The number of cases of congestive splenomegaly studied by the Spleen Clinic that have had splenectomy now totals fifty-five. Sixty per cent (thirty-three cases) of the entire group have had a proven obstructive factor as a possible basis for the portal hypertension.

Under the general classification of congestive splenomegaly we have continued to use the following groupings and sub-groupings:

I Obstructive factor known

A Cirrhosis of the liver

- a Laennec's cirrhosis
- b Unclassified cirrhosis
- c Cirrhosis due to schistosomiasis mansoni

B Thrombosis of the splenic vein

C Cavernomatous transformation of the portal vein

D Stenosis of the portal vein

II Obstructive factor undetermined

The results of splenectomy and the long-term follow-up will now be detailed group by group under the separate disease headings (Charts I and II) as just outlined. These cases have regularly been examined and complete blood studies made at least once a year since operation.

I Obstructive factor known

A Cirrhosis of the liver

a Laennec's cirrhosis

Fourteen cases of this type were operated upon. The immediate hospital mortality included four cases or 28 per cent. The causes of death were shock (1), hematemesis (1), hepatic insufficiency (2).

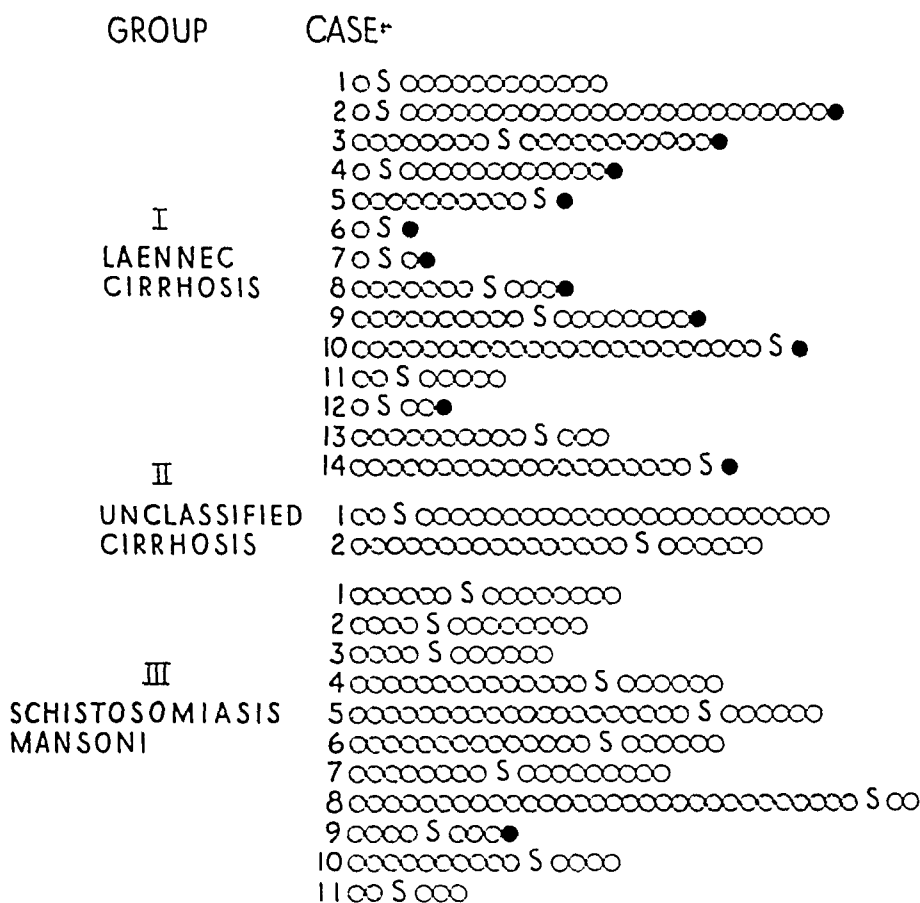
Seven late fatalities occurred at periods varying from five months to thirteen years. Death in all cases followed hematemesis, or cholemia with or without ascites.

The three survivors have been well to date for periods of one and a half years, five years, and six years, respectively. These poor results are at distinct variance with those found in the succeeding groups.

b Unclassified cirrhosis

Two cases are included in this grouping, both have done exceptionally well, one for three years and one for twelve years following operation.

# CONGESTIVE SPLENOMEGALY (BANTI'S SYNDROME) RESULTS OF SPLENECTOMY



## Cause of Death

Group I \*2 5 8 - Hematemesis  
 \*3 4 7 9 10 12 14 - Hepatic Insufficiency  
 \*6 - Post-operative Shock

Group III \*9 - Hematemesis

Chart I

- 1 Each circle represents six months in the clinical course
- 2 The letter S indicates time of splenectomy during the entire period patient was followed
- 3 Clear circles denote asymptomatic periods. Shaded circles denote periods with symptoms. Black circles denote death.

Chart II (refer to key under Chart I)

c Cirrhosis due to schistosomiasis mansoni\*  
Eleven cases of this disease with associated Banti's syndrome have had splenectomy. The mode of infection and the pathology of schistosomiasis are now well known. Faust, Jones, and Hoffman<sup>10</sup> have shown that the maturing phase of the parasite in the human host takes place in the hepatic

portal and mesenteric veins Following the deposition of eggs in the liver, a pseudo-tubercle or fibrous nodule is formed If the infestation is sufficiently heavy, a severe form of cirrhosis results Coupled with this cirrhosis is a splenomegaly, and with the splenomegaly there is often a blood picture similar to that in Banti's syndrome Oddly enough, the striking similarity of Banti's disease to the late visceral stage of schistosomiasis mansoni is one that has received scant mention Bonelli<sup>11</sup> drew the clinical comparison but concluded that the Banti-like picture in late schistosomiasis was on the basis of a toxin of intestinal origin Girges<sup>12</sup> with his extensive experience in Egyptian splenomegaly includes Banti's disease as a differential diagnosis of the late stage of the disease A particularly interesting feature of our experience in these cases is that prior to operation in several of them a clinical diagnosis of Banti's disease was made and only following liver biopsy was the exact nature of the lesion ascertained Campbell<sup>13</sup> in a recent publication from China has expressed the belief that most cases of Banti's disease in the Orient are really the late stage of schistosomiasis There has been no operative mortality in our eleven cases The only patient who had hematemesis prior to operation remained well for a period of two and a half years after operation and then suddenly succumbed to a hematemesis All the remaining ten patients are very well and have been followed for periods varying from two to four years

B Thrombosis of the splenic vein

We have had three cases of Banti's syndrome associated with splenic vein thrombosis All had an uneventful postoperative recovery and are well at ten months, five and a half years, and six years, respectively

C Cavernomatous transformation of the portal vein

We have had two examples of this rare condition Both cases had the typical clinical picture of Banti's syndrome with evidence of bleeding from esophageal varices In each instance hematemesis was the cause of death following operation — in the first case, two days after operation, and in the second instance,

\* A more detailed and complete report of the association of Banti's syndrome in schistosomiasis and the results of splenectomy in this disease, is in press

nine months after operation. Of particular interest to us is the fact that the liver was normal in each of these cases proven by autopsy, hence it is obvious that hematemesis is not necessarily the sequel of cirrhosis but can be a fatal issue in the presence of obstructive lesions other than cirrhosis. One of these cases was particularly instructive to us because prior to operation all the liver function tests gave normal values, at operation the liver grossly appeared normal and the liver biopsy likewise showed normal liver structure. We therefore classified this as one of the cases in which the obstructive factor was undetermined. It was only when the patient died nine months later that autopsy demonstrated the obstructive factor at the beginning of the portal vein. Klemperer<sup>14</sup> reported one such case and was able to collect twenty-three similar examples in the literature. His patient, as ours, also had undergone a splenectomy for supposed Banti's disease several years prior to death.

#### D Stenosis of the portal vein

This is a recent addition to our list of possible lesions causing portal congestion. We have had one patient with this unusual condition. At operation no obstructive factor was demonstrated. The liver biopsy was normal. Following operation the patient had six hematemeses over a period of thirteen years with finally a fatal hemorrhage. At necropsy there was no cirrhosis but a stenosis of the portal vein was present near its origin.

#### II Obstructive factor, undetermined

Our last series in the congestive splenomegaly group includes twenty-two cases in which the obstructive factor could not be demonstrated at operation. Three died in the postoperative period, a mortality of 13.6 per cent. The cause of death included shock (1), hepatic insufficiency (2).

Only one late death occurred and this two years and two months after operation of hematemesis.

Two died several years after operation of an unrelated disease. Of the remaining sixteen, thirteen have been entirely well for periods varying from two months to eighteen years. However there are three patients still living who have had a miserable course punctuated by repeated severe hematemesis over periods of three years, four years and two and a half years respectively.



## SUMMARY

In a group of fifty-five cases, similar characteristics were apparent in all, to warrant a diagnosis of congestive splenomegaly, or so-called Banti's syndrome. Evidence has been presented to show that portal hypertension exists as a common factor in a variety of different clinical entities. Each of these various diseases is capable of producing chronic portal stasis.

The indications for splenectomy in congestive splenomegaly and the long term prognosis are dependent on the nature and severity of the obstructive factor. Obviously, splenectomy is contraindicated in cases of progressive decompensated liver disease. The late results in our cases with Laennec's cirrhosis, portal vein occlusion or stenosis, have been extremely poor. The results in other forms of cirrhosis, splenic vein thrombosis, and the group in which the obstructive factor was undetermined have been most gratifying. Hematemesis as a postoperative symptom is usually a grave prognostic omen.

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# DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS IN THE MANAGEMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA\*

R. H. EGERTON ELLIOTT

**I**N 1936, a report<sup>1</sup> was published from the Spleen Clinic of the Presbyterian Hospital on the results of the treatment of purpura hemorrhagica by both splenectomy and conservative therapy. The object of this present paper is to bring those results up to date and, in addition, to relate some of the salient features of the diagnosis and management of this disease as it is seen in the spleen clinic.

There are certain elementary facts about purpura in general and thrombocytopenic purpura in particular which should be constantly borne in mind in any consideration of the management of the disease under discussion. It therefore seems advisable to review briefly the more important of these facts before proceeding further.

In the vast majority of instances in which it is encountered, purpura represents a symptom-complex rather than a disease entity. The frequency of its occurrence as such is attested by the fact that it may appear in the course of many common ailments. Under these circumstances, it is referred to as a "secondary" or "symptomatic" purpura.

The term "primary" or "idiopathic" purpura is reserved for those infrequent instances in which no associated disease process or cause for the symptom-complex can be found. The relative rarity of this latter group becomes apparent when it is considered that out of approximately 700 purpuras which have passed through the spleen clinic, only forty-two have been classified as "primary" or "idiopathic."

## SECONDARY PURPURA

The secondary purpuras then are those for which there is thought to be an assignable cause. They are the purpuras which occur with

\*From the Department of Surgery, Columbia University College of Physicians and Surgeons, the Spleen Clinic of the Presbyterian Hospital, Denver, Colorado. Received for publication, December 1, 1938. Graduate Fellowship.

infections, with poisoning by toxic agents with nutritional deficiencies and with certain disease processes affecting the reticulo-endothelial and hematopoietic systems. According to whether the platelet count is reduced or not they may be subdivided into secondary purpuras without thrombocytopenia and secondary purpuras with thrombocytopenia.

Secondary purpura without thrombocytopenia is encountered with considerably more frequency than the thrombocytopenic variety. While it may be associated with any of the previously mentioned etiologic factors, it is most commonly seen in the course of acute infections. In most instances, its recognition as a secondary purpura is attended with little difficulty.

Secondary purpura with thrombocytopenia, on the other hand, may at times be exceedingly difficult to differentiate from a primary or idiopathic purpura. It likewise may occur in conjunction with any of the aforementioned etiologic factors, but in our experience is most frequently seen in disturbances of the hematopoietic system, in particular the aplastic anemias and the leukemias.

The important point to be remembered about the management of the secondary purpuras as a whole is that therapy should be directed primarily at the disease process underlying the purpura. That the performance of splenectomy for the relief of hemorrhagic manifestations in this group is emphatically contraindicated and often attended by tragic consequences, will be apparent when we come to discuss our results.

### PRIMARY PURPURA

Bearing in mind the foregoing considerations, it will be realized that the diagnosis of primary or idiopathic thrombocytopenic purpura can only be reached by the careful exclusion of all factors known to cause purpura. Unfortunately, those disease processes which most frequently cause an associated thrombocytopenic purpura are often the most difficult of recognition, as, for example, an aplastic anemia or an aleukemic leukemia. For this reason, the *sine qua non* of diagnosis is an accurate hematologic interpretation of the blood findings.

It also goes without saying that other common pitfalls in diagnosis can only be avoided by the taking of a careful history, with especial reference to dietary habits and drug idiosyncrasies, and by an exhaustive search for foci of infection in the teeth, tonsils, sinuses and other

common locations In this connection, it should also be borne in mind that metastatic invasion of the bone marrow from an unsuspected primary focus of malignancy may occasionally cause thrombocytopenic purpura In our records, we have four such cases, all of them proven at necropsy

### NATURAL HISTORY OF THE DISEASE

Primary or idiopathic thrombocytopenic purpura may occur at any age, but in our experience is most frequently seen before the fourth decade It is uncommon beyond the fifth decade and rare in the aged If untreated, its course in the adult is characterized by chronicity and recurrence

It is perhaps fitting at this point to say a word about the occurrence of this disease in children Though the great majority of patients who attend the spleen clinic are adults, through the co-operation of the Hematology Clinic of the Babies Hospital we have of late years been privileged to see an increasing number of individuals in the early age groups Furthermore, as these patients mature, they are automatically transferred for their future follow-up to our clinic We have, therefore, been afforded the opportunity of obtaining unusually complete follow-ups on many of our cases

From a perspective of the disease so obtained and from our frequent contact with the members of the hematologic group of the Babies Hospital, we have come to feel that thrombocytopenic purpura in children generally presents a different picture and a different problem from that observed in adults

In childhood, idiopathic thrombocytopenic purpura tends to be a self-limited disease, characterized by spontaneous recovery In relatively few instances does it persist into adulthood as a chronic, recurrent ailment According to McLean, Kreidel and Caffey<sup>2</sup> it affects boys twice as frequently as girls

In adults, on the other hand, chronicity and recurrence in the untreated case are the rule, rather than the exception Furthermore, our figures for sex incidence would seem to indicate that the disease occurs principally in females, for, out of forty-two patients, thirty-seven or 88 per cent were women and only five or 12 per cent men It is of interest that at the onset of the disease four of the five males were under fourteen years of age and the fifth had not reached his twenties

## CLINICAL PICTURE

The disease, then, is generally seen in young females in the second or third decade of life. A variable history of easy bruising, of bleeding into the skin and of hemorrhage into, or from the mucous membranes may be given. Intractable menorrhagia is a frequent and distressing symptom. In advanced cases hematuria, melena, blurring of vision and symptoms due to cerebral hemorrhage are not uncommon.

On physical examination, evidence of hemorrhage into the skin or mucous membranes or both, will be present to a variable extent. If the patient is in an active phase of the disease, a typical muddy pallor may be apparent. The gums are often characteristically soft, swollen and spongy, the teeth caked with clotted blood. In addition, in the far advanced disease intra-ocular hemorrhages and reflex changes may be present.

The existence of a palpable spleen is unlikely in early cases but in individuals who have had the disease over a long period of time, its tip can occasionally be appreciated just below the costal margin. In our series of forty-two cases, the organ was felt in ten instances, and in only one of these was the disease in its early stages. It should be emphasized, however, that the presence of any considerable degree of splenomegaly is a point against the diagnosis of idiopathic thrombocytopenic purpura. The remainder of the physical examination will generally be non-contributory.

## LABORATORY FINDINGS

With regard to the various laboratory findings, an anemia of the secondary type is usual, but is never in excess of that due to blood loss. The white and differential blood counts are normal except in severe cases with widespread hemorrhage, when a polymorphonuclear leukocytosis may be expected. The presence of a leukopenia should cast immediate doubt upon the diagnosis. More often than not, it indicates the presence of an underlying aplastic anemia or other blood dyscrasia. The platelets, of course, are markedly reduced in number and may even be absent on direct examination.

In the classic case, the bleeding time is prolonged, the clotting time normal and the clot retraction delayed or absent. Occult or frank blood may be present in the stool, urine or gastric content. The tourniquet test is usually positive.

Of even more importance than the latter, the capillary resistance, as measured by the Dalldorf suction apparatus, will be reduced in proportion to the severity of the disease. This latter test, which was the subject of a recent communication<sup>7</sup> from this clinic, has in our hands proved extremely useful in estimating the activity of the disease. In this respect, we believe it to be frequently of more value than the platelet count. A summary of the majority of the aforementioned findings will be found in Tables I and II (See next page)

#### PATHOLOGY

At operation, some degree of enlargement of the spleen was reported in all but eight of our cases. Typically, however, the spleen is small and soft in comparison with other varieties of splenomegaly.

There is no general agreement among authors on the existence of a characteristic pathological picture in the spleens removed from individuals suffering from purpura hemorrhagica. In 1937, Nickerson and Sunderland<sup>4</sup> of the Mallory Institute of Pathology in Boston reported the presence of fairly constant pathologic change in the spleens from eleven cases of this disease.

They found that in every instance, the germinal centers were enlarged and active and that megakaryocytes were present in the sinuses of the pulp. Furthermore, the number of neutrophile or eosinophile polymorphonuclear leukocytes was increased in the pulp in all but two cases. These changes they regarded as characteristic of idiopathic thrombocytopenic purpura hemorrhagica.

We are not prepared to say more than that the majority of the spleens removed from our cases have shown changes consistent with these findings.

#### MANAGEMENT

Following the admission of a case of purpura to the hospital the platelet count and capillary resistance are watched closely. An attempt is made to improve the general condition of the patient by ordinary supportive measures and, when indicated, by repeated transfusions. While these steps are being taken a careful search for foci of infection is undertaken, consultants being used freely in the process.

After a thorough-going period of study, during which all other diagnostic possibilities have been ruled out to the satisfaction of the

TABLE I

INITIAL BLOOD PICTURE AND SEVERITY ON ADMISSION IN GROUP  
IN WHICH OPERATION WAS PERFORMED

Case	Severity	Platelets	Bleeding Time	Clotting Time	Clot Retraction	Capillary Resistance	Tourniquet Test	Hb. % (Sml)	Rbc	Wbc	Pmn	Lym	Other Cells
1	Moderate	20,000	5'	25'*	Prolonged	Not done	Not done	Not done	3 2	12 2	55	27	18
2	Moderate	Too few to count	9'	8'	Prolonged	Not done	Not done	75	4 1	10 3	59	21	17
3	Mild	15,000	3' 30"	4'	Normal	Not done	Not done	53	3 3	10 9	71	23	3
4	Severe	28,000	58'	1' 30"	Not done	Not done	Not done	21	1 9	21 0	81	10	6
5	Moderate	6,000	10'	3'	Prolonged	Not done	Positive	65	3 7	8 7	60	32	8
6	Moderate	15,000	5' 30"	3'	Prolonged	Not done	Not done	56	3 1	9 9	73	21	6
7	Severe	6,000	7'	5'	Not done	Not done	Not done	33	3 2	5 5	85	10	5
8	Moderate	19,000	15' +	5'	Prolonged	Not done	Positive	75	5 3	8 6	52	32	16
9	Severe	15,000	4'	5' 30"	Not done	Not done	Not done	32	2 2	5 7	65	25	10
10	Moderate	26,000	15' 30"	2' 45"	Prolonged	Not done	Positive	75	3 8	6 9	72	16	12
11	Severe	60,000	25' +	7'	Normal	Not done	Not done	60	2 9	8 8	61	28	8
12	Moderate	5,000	4' 37"	3' 20"	Prolonged	10	Positive	89	4 9	8 1	88	6	6
13	Severe	10,000	15' +	3'	Prolonged	10	Not done	55	3 0	7 5	75	20	5
14	Severe	26,000	13' 35"	1' 55"	Prolonged	10	Positive	102	6 2	15 7	78	18	7
15	Mild	23,000	20' +	3'	Not done	10	Not done	10	4 1	18 0	60	33	10
16	Mild	15,000	3' 15"	4' 8"	Not done	15	Not done	90	4 6	8 0	55	35	14
17	Moderate	20,000	20'	6'	Prolonged	20	Not done	57	4 3	6 2	66	20	8
18	Moderate	16,000	15' +	4'	Not done	10	Not done	76	3 4	12 4	72	20	1
19	Mild	10,000	Not done	Not done	Not done	15	Positive	92	4 8	6 1	51	15	3
20	Moderate	31,000	3'	2' 30"	Prolonged	10	Not done	55	4 6	9 1	62	35	1
21	Moderate	22,000	1'	5' 15"	Not done	10	Positive	38	2 2	7 0	78	11	8

\* Accuracy of this value open to question

TABLE II

INITIAL BLOOD PICTURE AND SEVERITY ON ADMISSION IN GROUP  
IN WHICH OPERATION WAS NOT PERFORMED

Cases	Severity	Ht-leukts	Bleeding Time	Clotting Time	Clot Retraction	Capillary Resistance	Tourniquet Test	Hb % (Sulih)	Rbc	Wbc	Plmn	Lym	Other Cells
1	Severe	Too few to count	36'	5'	Prolonged	Not done	Not done	28	27	175	79	19	2
2	Moderate	15,000	21' 20"	2' 30"	Prolonged	Not done	Positive	71	11	86	51	37	9
3	Moderate	35,000	28' 30"	3'	Prolonged	Not done	Positive	70	31	95	59	36	5
4	Mild	15,000	15'	1'	Prolonged	Not done	Positive	100	55	55	15	50	2
5	Mild	20,000	1' 30"	5' 30"	Normal	Not done	Negative	15	31	100	73	19	8
6	Moderate	8,000	33'	3'	Prolonged	Not done	Not done	78	11	105	66	22	12
7	Mild	28,000	9' 15"	3'	Prolonged	Not done	Positive	85	39	81	78	11	8
8	Moderate	8,000	1' 30"	2' 15"	Not done	Not done	Positive	88	51	69	72	16	12
9	Moderate	6,000	12'	2' 30"	Not done	Not done	Not done	63	39	58	60	26	11
10	Moderate	12,000	6' 30"	2' 30"	Prolonged	Not done	Not done	75	22	72	17	18	5
11	Mild	10,000	1' 30"	5' 15"	Prolonged	Not done	Not done	76	11	53	65	31	1
12	Mild	20,000	1'	Not done	Normal	Not done	Negative	85	17	86	62	31	1
13	Mild	10,000	11' 15"	8'	Not done	20	Positive	100	48	57	63	31	3
14	Mild	6,000	5' 40"	2' 25"	Prolonged	15	Positive	85	50	117	70	27	3
15	Moderate	22,000	9' 40"	2' 30"	Prolonged	Not done	Positive	90	15	93	52	15	3
16	Moderate	5,000	7' 55"	2' 23"	Prolonged	Not done	Negative	95	17	101	73	21	6
17	Severe	11,000	6' 30"	1'	Prolonged	30**	Not done	88	15	96	19	19	2
18	Moderate	20,000	1' 15"	5'	Normal	10	Positive	55	26	60	69	21	10
19	Mild	10,000	15'	1' 15"	Normal	15	Not done	92	56	100	71	22	1
20	Mild	6,000	7' 30"	1' 30"	Not done	15	Not done	86	50	89	75	15	10

\*\* Accuracy of this value open to question



members of the spleen clinic, splenectomy is advised. In this connection, it may be said that, when possible, we prefer to remove the spleen during a remission of the disease. Immediate splenectomy is performed only as an emergency or semi-emergency measure.

In our experience, as we believe our results will show, splenectomy offers a greater hope of the complete arrest of purpura hemorrhagica than any other form of therapy. We have tried at various times vitamin C, sesame oil, progynon, oil of turpentine, ultraviolet light and multiple transfusions without noticeable success.

While we have not ourselves used snake venom, seven of our twenty-two operated cases had received this form of therapy before coming to the spleen clinic. In none did more than temporary relief result. Therefore we are led to believe that this form of therapy is of no permanent benefit in idiopathic thrombocytopenic purpura. In this connection, it may be of interest to note that all of the seven above-mentioned cases have been asymptomatic since splenectomy.

Immediately prior to operation, a transfusion needle is placed in the patient's arm. Throughout the operative procedure a compatible blood donor is held in readiness in an adjacent room. Platelet counts and capillary resistance determinations are performed before, during and shortly after removal of the spleen. It is not unusual for all bleeding to cease and for both the capillary resistance and platelet count to show appreciable increments immediately after removal of the spleen, but before the abdominal closure is completed. In the typical case, there is a cessation of the bleeding tendency and an abrupt rise in both of the latter values within the first twenty-four hours after operation. In most instances, the capillary resistance tends to rise more rapidly than the platelet count.

The postoperative course of these patients frequently tends to be stormy. Persistent distention and a remittent type of fever have been the two most common complications in our series of cases. The etiology of the fever has in all instances remained a mystery. We suspect that it may be due to a thrombophlebitis of the splenic vein. In at least two cases in which it occurred, it subsided abruptly following the administration of prontosil. It should be remembered, however, that in purpura this drug must be used with more than ordinary caution in view of its occasional detrimental action on the blood elements.

Despite the possible complications of the postoperative period and

the increased hazards encountered in operating upon individuals with this disease, we have no operative deaths to report in this group. In this connection, it cannot be emphasized too strongly that operation should only be attempted by an unusually well qualified surgeon.

### RESULTS

Up to October 1, 1938, forty-two patients with idiopathic thrombocytopenic purpura had been treated in the Spleen Clinic of the Presbyterian Hospital. Twenty-two of these individuals had undergone splenectomy. The remaining twenty had been treated conservatively.

One patient in the group undergoing splenectomy was operated upon too recently to warrant inclusion in the following tables. Consequently this case does not appear in Chart I which depicts the follow-up results in twenty-one operative cases.

In thirteen of these twenty-one cases, the disease appears to be permanently arrested. In five, because of some trivial incident in an otherwise perfect follow-up, it has been designated as markedly improved. Therefore the results in eighteen, or 85.7 per cent of this group may be said to have been eminently satisfactory.

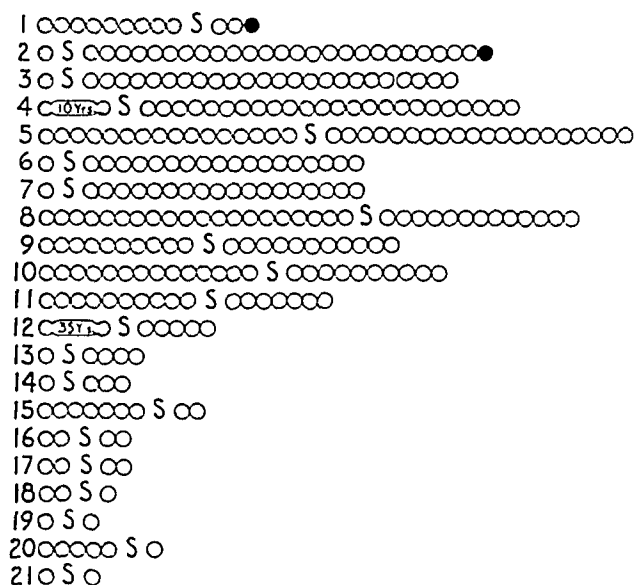
Of the three remaining cases subjected to splenectomy, two have been improved, but by no means symptom-free, since operation, and one has died of the disease. This death occurred eighteen months after operation and was apparently caused by cerebral hemorrhage. Unfortunately, permission for an autopsy could not be obtained. The one other death in the operative group occurred in an individual whose purpura had been completely arrested for thirteen years. It was due to an unrelated, intercurrent disease.

The follow-up results on the twenty conservatively treated cases of idiopathic thrombocytopenic purpura are shown in Chart II. In only two of the twenty cases in this group does the disease appear to be completely arrested. In none can it be classified as markedly improved. Therefore, conservative therapy can be said to have been entirely successful in only 10 per cent of the group.

The follow-up reports on the eighteen patients remaining in this group may be summarized as follows. In four instances the disease is still present, but has shown some degree of improvement, in thirteen instances, its initial severity remains unchanged, in one instance it proved fatal, the patient having died in an acute flare-up of the disease.

# IDIOPATHIC THROMBOCYTOPENIC PURPURA CESSATION OF ACTIVITY FOLLOWING SPLENECTOMY

## CASE\*



### Cause of Death

\*1 - Cerebral Hemorrhage

\*2 - Unrelated Disease

Chart I

- 1 Each circle represents six months in the clinical course
- 2 The letter S indicates time of splenectomy during the entire period patient was followed
- 3 Clear circles denote asymptomatic periods Shaded circles denote periods with symptoms Black circles denote death

At necropsy, death was found to have been due to cerebral hemorrhage

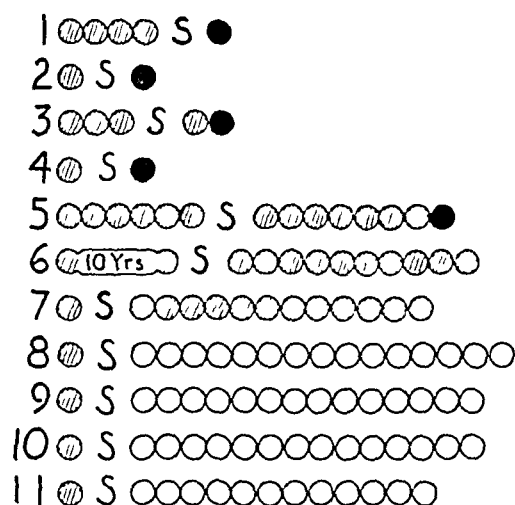
It is therefore apparent that in these eighteen cases, which comprise 90 per cent of the conservatively treated group, the follow-up results were unsatisfactory

If the operative and non-operative groups are compared (Table III), it will be seen that satisfactory results were obtained in 85.7 per cent of the operative and in only 10 per cent of the non-operative. On the other hand, splenectomy yielded unsatisfactory results in only 14.3

\* Death due to purpura

# SPLENECTOMY IN SECONDARY PURPURA

CASE#



- #1,7-Undiagnosed Disease
- #2,6 Aplastic Anemia
- #3 - Miliary Tbc
- #4 - Acute Rheumatic Fever
- #5 - Osteosclerotic Anemia
- #8 - Gold Thiosulphate Poisoning
- #9,10,11 - Transient Infection

Chart III (refer to key under Chart I)

per cent of the cases so treated, while conservative therapy failed to produce satisfactory results in 90 per cent of the cases treated by this method. It is on this comparison that we base our contention that splenectomy is the most effective therapeutic measure at present employed in the treatment of idiopathic thrombocytopenic purpura. An essentially similar conclusion was reached by Wintrobe, Hanrahan and

Thomas<sup>5</sup> of Johns Hopkins in their paper on purpura hemorrhagica published in 1937

### RESULTS OF SPLENECTOMY IN ATYPICAL PURPURA

Chart III depicts the follow-up on eleven cases of atypical purpura which were subjected to splenectomy. In every instance the purpura proved, subsequent to operation, to be of the secondary, or symptomatic type.

Satisfactory results followed operation in only four instances. In one patient, the bleeding tendency has been improved slightly and in another, it does not seem to have been affected by operation. The remaining five patients are dead. One of these patients died before leaving the operating table, one succumbed to a postoperative complication and the remaining three died after leaving the hospital of diseases to which the purpura was apparently secondary.

In three of the four cases benefited by operation, the purpura was associated with acute, transient infection. In the fourth it was apparently secondary to poisoning by gold thiosulphate. It seems not unlikely therefore, that, had the associated etiologic factors in these four cases been eradicated prior to splenectomy, the bleeding tendency might have ceased without operative interference.

In the seven cases in which splenectomy was followed by unsatisfactory or fatal results, the purpura later proved to be associated with an aplastic anemia in two instances, with an undiagnosed disease process in two instances, and with an acute rheumatic carditis, a military tuberculosis and an osteosclerotic anemia in the remaining three respective instances.

This group of cases is presented to illustrate the diagnostic pitfalls, futile operations and high mortality so frequently encountered among the atypical purpuras.

### CONCLUSIONS

1. In the vast majority of instances in which it is encountered purpura represents a symptom-complex rather than a disease entity.
2. In children thrombocytopenic purpura generally presents a different picture and a different problem from that observed in adults.
3. In adults primary or idiopathic thrombocytopenic purpura is a relatively rare condition occurring principally in women. Its course

if untreated, is characterized by chronicity and recurrence

4 The diagnosis of primary or idiopathic thrombocytopenic purpura should only be made after all of the etiologic factors known to be associated with the appearance of secondary purpura have been carefully excluded

5 When performed by an experienced surgeon, splenectomy is the most effective form of therapy at present employed in the treatment of idiopathic thrombocytopenic purpura

6 The removal of the spleen for the relief of hemorrhagic manifestations in cases of atypical or secondary purpura is emphatically contraindicated and is attended by a high incidence of disappointing and fatal results

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## PROCEEDINGS OF ACADEMY MEETINGS

## STATED MEETINGS

NOVEMBER 3—*The New York Academy of Medicine* Executive Session—a] Reading of the minutes, b] Report of Nominating Committee, c] Report on election of members ¶ Papers of the evening (Graduate Fortnight)—a] The Wesley M Carpenter lecture Hemophilia, William H Howell, Baltimore, b] Classification and treatment of purpura, Nathan Rosenthal, Associate in Medicine and Hematologist, The Mount Sinai Hospital

NOVEMBER 17—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The Second Harvey Lecture, The Significance of the Albumin Fraction of Serum, A Ashley Weech, Associate Professor of Diseases of Children, College of Physicians and Surgeons

DECEMBER 1—*The New York Academy of Medicine* Executive Session—a] Reading of the minutes, b] Election of Academy Officers ¶ Papers of the evening—Symposium on serum therapy in pneumonia—1] Present status of serum therapy, Russell L Cecil, Professor of Clinical Medicine, Cornell University Medical College, b] Results with rabbit serum, Colin MacLeod (by invitation), Associate, The Rockefeller Institute for Medical Research, c] Program for meeting the pneumonia situation, Wheelan D Sutliff (by invitation), Assistant Director, Pneumonia Control Division, Bureau of Laboratories, Department of Health, Discussion by Edward Tolstoi, Jesse G M Bullock, Ralph S Muckersfuss (by invitation)

DECEMBER 15—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The third Harvey Lecture Heat Loss from the Human Body, Eugene T Du Bois Professor of Medicine, Cornell University Medical College

JANUARY 5—*The New York Academy of Medicine* Executive Session—a] Reading of the minutes, b] Amendment to Constitution and By-Laws, c] Presentation of Diplomas ¶ Presentation of annual reports (to be read by title) The Council, The Trustees, The Treasurer, Committees ¶ Address of the retiring president, James Alexander Miller ¶ Address of the incoming president, Malcolm Goodridge ¶ Papers of the evening Symposium on chronic gastritis—a] Recent advances in diagnosis by gastroscopy, Rudolf Schindler, Associate Professor of Medicine, The University of Chicago, b] Clinical aspects, Burrill B Crohn, Associate in Medicine, The Mount Sinai Hospital ¶ Report on election of members

JANUARY 19—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The fourth Harvey Lecture, "Proteins as Chemical Substances and Biological Components," Edwin J Cohn, Professor of Biological Chemistry, Harvard Medical School

## SECTION MEETINGS

NOVEMBER 8—*Joint Meeting, Neurology and Psychiatry and the New York Neurological Society* Papers of the Evening—1] Brief manic depressive cycle as in epileptic process, Richard M Brierley, Albert Rosner (by invitation) Discussion by Nolan D C Lewis (by invitation), b] Pathological laughing and crying, a neuro-anatomical neuro-physiological and psychological study, Charles Divison Harold Kellman (by invitation), Discussion by Henry Altop Pile, Nolan D C Lewis (by invitation) c] Some aspects of the biochemistry of alcoholic delirium Herman Wortis (by invitation), S Bernard Wortis Paula Frank (by invitation), Norman Tollide (by invitation) Karl M Bowers (by invitation) Discussion by Foster Kennedy

*Dermatology and Syphilology* This Section held no meeting because of conflict in date with the Graduate Fortnight

*Surgery* This Section held no meeting because of conflict in date with the Graduate Fortnight

NOVEMBER 9—*Historical and Cultural Medicine* Reading of the Minutes ¶ Papers of the Evening—a] Sir Benjamin Ward Richardson's Hygeiopolis, and Jules Verne's Franceville, Ramsey Spillman, Discussion by Haven Emerson, b] The laryngeal cancer of Frederick the Third of Germany, George T Pack, Discussion by James Ewing ¶ General Discussion ¶ Executive Session

NOVEMBER 10—*Pediatrics* On account of the meeting of the American Academy of Pediatrics at Rochester this month, there was no meeting of the Pediatric Section at the Academy

NOVEMBER 15—*Medicine* Reading of the Minutes ¶ Papers of the Evening—a] The pathology and clinical manifestations of polyneuritis, I S Wechsler Discussion by Foster Kennedy, b] The role of heavy metals and infections in polyneuritis, Leon H Cornwall, Discussion by E D Friedman, c] Evaluation of vitamin B, (thiamine chloride) in the treatment of polyneuritis, Martin Vorhaus, Discussion by Norman Jolliffe

NOVEMBER 16—*Otolaryngology* Reading of the Minutes ¶ Papers of the Evening Symposium on otitic meningitis—a] Diagnosis—Bacteriological, A A Eggeston, Differential, I G Dwyer, b] Avenues of infection, M F Jones c] Operative treatment, Wesley Bowers, d] Chemotherapy, Emanuel Appelbaum ¶ Discussion, Josephine B Neal, Philip D Kerrison

NOVEMBER 16—*Genito-Urinary Surgery* Reading of the minutes ¶ Papers of the evening—a] Endoscopic photography, Andrew Peterson (by invitation), b] Case report aplastic kidneys, J K DeVries, c] New aspects in the treat-

ment of vaginitis in children, Rose Andre (by invitation), d] Prevention of recurrent renal stone by calyceal resection, Francis Twinem, e] Treatment of post-operative and inoperable urological tuberculosis, Stanley Wang (by invitation), f] Urethrogams in infants and children, Paul M Butterfield, g] Report of results of certain newer plastic operations in urology, Oswald S Lowesley ¶ General discussion

NOVEMBER 18—*Orthopedic Surgery* Instead of the regular meeting of Orthopedic Surgery at the Academy, the members met in Philadelphia at a joint meeting with the Philadelphia Orthopedic Club of Jefferson Medical College

NOVEMBER 21—*Ophthalmology* Instructional hour—Perimetry of chiasmal lesions, Ralph I Lloyd ¶ Slit lamp demonstration, Milton L Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Reading of the minutes (8 30) ¶ Report of committees ¶ Presentation of cases—a] Recurrence of ocular hypertension eighteen years after an Elliot trephining, Mark Schoenberg, b] A report on the use of sulfanilamide in the treatment of inclusion conjunctivitis, Phillips Thygeson (by invitation), c] Grenz ray in ophthalmology, Raymond Pfeiffer, Discussion by Gustave Bucky (by invitation) ¶ Papers of the evening—Interpretation of fundal changes associated with arterial hypertension, Walter I Lillie (by invitation)

NOVEMBER 22—*Obstetrics and Gynecology* Presentation of a case—A case of fibromyosis uteri, Frank Spielman (by invitation), Discussion by Samuel H Gust ¶ Papers of the evening—a] Sterilization in the female (Madlener technic), Erwin von Graff (by invitation), Discussion by Robert L Dickinson, William H Cary (by invitation), Mortimer N Hyams, b] Pitfalls of version, Milton G Potter, Buffalo (by invitation), Discussion by William E Studdiford, William E Caldwell ¶ General discussion

DECEMBER 2—*Surgery* Reading of the minutes ¶ Presentation of case reports—*a*] An abdominal reflex complicating anesthesia, Thomas H Russell, Discussion by M C Peterson (bv invitation), *b*] Toxic effects of carbon dioxide, Wallace B Murphy (bv invitation), Discussion by B B Lennon (bv invitation), *c*] Untoward reaction with avertin, Henry W Cave, Discussion by Lewis S Booth (bv invitation), *d*] Atelectasis complicating surgery, Louis Rene Kaufman Discussion by Donald E Brace, *e*] Anesthetic management during ruptured ectopic pregnancy, William E Studdiford, Discussion by John Adriani (bv invitation) ¶ Papers of the evening—*a*] Newer anesthetic agents, Paul M Wood Discussion by T Drysdale Buchanan (bv invitation), *b*] Newer anesthetic techniques, E A Rovenstine, Discussion by T Drysdale Buchanan (bv invitation) ¶ General discussion

DECEMBER 6—*Dermatology and Syphilology* Reading of the minutes ¶ Presentation of cases—*a*] Mt Sinai Hospital *b*] Miscellaneous cases ¶ General discussion ¶ Executive session

DECEMBER 8—*Pediatrics* Presentation of case, Brittain F Payne ¶ Papers of the evening—*a*] Normal development of the eye through infancy and childhood, Willis Knighton, *b*] The responsibility of the pediatricians in regard to children's eyes, Brittain F Payne, *c*] Care of the eyes in acute contagious and infectious diseases, David Webster, *d*] Management of strabismus in infancy and childhood, Maynard Wheeler ¶ Discussion, John Dunnington, Le Grand H Hardy ¶ Executive session

DECEMBER 13—*Neurology and Psychiatry* Reading of the minutes ¶ Papers of the evening—*a*] Pathologic aspects of some forms of trauma to the brain and spinal cord, Lewis Stevenson, Discussion by Benjamin M Vance, Milton Helpner *b*] The place of Roentgen ray in the diagnosis of head injuries, Cornelius Dyke Discussion by Leo M Davidoff, Emanuel D Friedman *c*] A compara-

tive study of the dehydrating action of dextrose, sucrose, sodium chloride, sorbitol and caffeine as determined by changes in the cerebrospinal fluid, Jefferson Browder (bv invitation), Discussion by S Bernard Wortis

DECEMBER 16—*Orthopedic Surgery* Reading of the minutes ¶ Presentation of cases—*a*] Congenital subluxation of the fifth toe and its correction by a periosteocapsuloplasty operation, Leon Lintzounis, *b*] Cavernous angioma of the tibialis posticus muscle, Edgar D Oppenheimer ¶ Papers of the evening—*a*] Malignant giant cell tumor of the tibia, Case report, Samuel Kleinberg Discussion by Henry L Jaffe, *b*] The evolution of the spine fusion, M Beckett Howorth, Discussion by Mather Cleveland, *c*] Three and one-half years experience with the corkscrew bolt and some points regarding its insertion, Robert K Lippmann, Discussion by Philip Wilson ¶ General discussion ¶ Executive session

DECEMBER 19—*Ophthalmology* Instructional hour—Neurology of visual apparatus, George Arthur Blakeslee ¶ Slit lamp demonstration, Milton L Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Reading of the minutes (8 30) ¶ Presentation of cases—*a*] Gonioscopic apparatus, Donald W Bogart (bv invitation), *b*] A congenital type of endothelial dystrophy, Frederick H Theodore (bv invitation) *c*] A typical primary degeneration of the retina (retinitis pigmentosa sine pigmento) Report of three instances in a family of five children, Samuel P Oist *d*] Chorioretinitis of the macula Report of a case with an extension from the macula area quiescent at least twelve years Raymond Emory Meek *e*] Bacterial synergism in lid necrosis Report of a case, Isadore Givner ¶ Paper of the evening—Fundus evidence of ocular injury, Arthur I Bedell

DECEMBER 20—*Joint Meeting Medicine and the New York Diabetic Association* Reading of the minutes ¶ Papers of the evening—*a*] Present status of protamine

zinc insulin therapy, Herman Linde (by invitation), b] Protamine zinc insulin A metabolic study of two severe cases of diabetes with comments on criteria for treatment, Edward Tolstoi, Discussion by Eugene J. Du Bois, George E. Anderson (by invitation), c] The management of diabetic acidosis and its accompanying "medical shock," H. Rawle Geyelin, Discussion by Louis Berman

#### DECEMBER 21—*Genito-Urinary Surgery*

Reading of the minutes § New instrument—A cystoscope holder, Arthur A. Rosenthal § Case report—Two unusual cases of diverticuli of the urinary bladder 1 Sidney Ritter § Paper of the evening—The influence of accessory renal vessels in certain cases of hydronephrosis, Hugh J. Jewett, Baltimore (by invitation) Discussion by Augustus Harris, George F. Hoch, Thomas J. Kirwin § General discussion

#### DECEMBER 21—*Otolaryngology*

Reading of the minutes § Papers of the evening—1] Deep infections of the neck, (1) Anatomy, John M. Lore, (2) Diagnosis and treatment, Henry B. Orton, (3) Discussion, Henry S. Dunning, J. F. Sherman Sheehin, b] Facial paralysis (1) Nerve graft operation, Thomas G. Tickle, (2) Plastic reconstruction, Clarence R. Straatsma (by invitation), (3) Discussion by J. H. Tenney (by invitation)

#### DECEMBER 27—*Obstetrics and Gynecology*

Presentation of cases—a] Puerperal sepsis, following spontaneous delivery, sulfanilamide treatment, A. C. Posner (by invitation), b] Pre-eclampsia-twins, Meyer Rosensohn, c] Diabetes-Cesarean section, A. J. Fleischer (by invitation), d] Carcinoma developing in teratoma of ovary, (1) Clinical, I. Smiley (by invitation), (2) Pathological, L. Auster (by invitation), e] Granulosa cell tumor of ovary, H. B. Schoenberg, Discussion by F. R. Smith § Lantern slide demonstration—1] X-Ray visualization of soft tissues of pregnancy at term, Meyer

Rosensohn, W. Snow, Discussion by J. R. Carty, Solomon Weintraub § Paper of the evening—1] Infectious diarrhea of newborn, Joseph Felsen, Discussion by Henry Heimann

#### JANUARY 3—*Dermatology and Syphilology*

Presentation of cases—1] New York University College of Medicine and Bellevue Hospital, b] Miscellaneous cases § General discussion § Executive session

#### JANUARY 6—*Surgery*

Reading of the minutes § Presentation of cases—a] Obstruction of the rectosigmoid by adhesions, Edwin B. Eckerson, Discussion by Edward J. Donovan, b] Colectomy and ileosigmoidostomy for multiple polyposis in a child 11 years of age, Irwin E. Siris, Discussion by John H. Morris, c] Fibrolipoma of the cecum, with ceco-colic intussusception and ulcerative colitis, Joseph H. Fobes, Discussion by Henry W. Cave, § Papers of the evening—1 Malignancy of the colon simulating other diseases, A. Lightstone, Discussion by William C. White, 2 A simplification of the perineal operation, Jerome Lanch, Discussion by Vincent Hurley, 3 Multiple stage operations in surgery of the colon, Ralph Colp, Discussion by William F. MacFee § General discussion

#### JANUARY 10—*Combined Meeting, Neurology and Psychiatry and the New York Neurological Society*

Papers of the evening—1] The treatment of depersonalization, Paul Schilder, Discussion by Manfred Sakel (by invitation), Louis Wender, b] A method for differentiating manic-depressive depressions from other depressions by means of parotid secretions, Edward I. Strongin, Leland E. Hinsie, Discussion by Karl M. Bowman (by invitation), Harold G. Wolff, c] Psychiatric disorders in fifty school teachers, James H. Wall (by invitation), Discussion by Robert B. McGraw, Leland E. Hinsie

#### JANUARY 11—*Historical and Cultural Medicine*

Reading of the minutes § Papers

of the evening—a] Obstetrics at the New York Almshouse and Bellevue Hospital Lantern slides, Claude Edy in Heaton, Discussion by William E Caldwell, b] Obstetric forceps from the Chamberlens to the present Lantern slides, Hervey C Williamson, Discussion by B P Watson, Andrew A Marchetti ¶ General discussion ¶ Executive session

JANUARY 12—*Pediatrics* Residents' night Papers of the evening—a] New York University Medical College, 'Subacute' pneumonia, Herbert Johnson, Bellevue Hospital (by invitation), Discussion opened by Edith M Lincoln, b] New York University Medical College, Meningitis sympathica as an onset of Pott's disease, Lawrence Slobody, Metropolitan Hospital (by invitation), Anthony Maffia, Metropolitan Hospital (by invitation), Josephine B Neal, Discussion opened by Reuel A Benson, c] Cornell University Medical College, Dysostosis multiplex, James M Hanks, New York Hospital (by invitation), Milton Berliner, Discussion opened by Samuel Z Levine, d] College of Physicians and Surgeons, Treatment of pneumococcal infections with 2-sulfamyl aminopyridine, Gilbert M Jorgensen, Babies Hospital (by invitation), Discussion opened by Rustin McIntosh, David Rutstein (by invitation), Henry Christian (by invitation)

JANUARY 16—*Ophthalmology* Instructional hour Local anesthetics Walter S Atkinson ¶ Slit lamp demonstration, Milton I Berliner Wendell L Hughes Girolamo Bonaccolto, Gordon M Bruce ¶ Reading of the minutes (8 30) ¶ Presentation of cases—1] Meningioma producing unilateral exophthalmos, James W Smith b] A calibrated nipple for contact lenses Joseph I Pascal c] Keratitis in Hurler's disease, Milton I Berliner d] A rare tumor of the orbit Color photomicrographs of biopsy material from orbit sternum and gland from neck Color photomicrographs showing blood picture William McLean Robert W Ward (by invitation) Wil-

liam E Youland (by invitation), e] Relation of vascular disease to retinitis A new clinico-pathological study (with slides), S A Agatston

JANUARY 17—*Medicine* Reading of the minutes ¶ Papers of the evening—a] Pneumonias other than pneumococcus pneumonia, Yale Kneeland (by invitation), Discussion by David D Rutstein, Medical Consultant, Bureau of Pneumonia Control, Albany (by invitation), b] Preliminary report of the use of sulfanilamide pyridine (M & B 693) in the treatment of lobar pneumonia, 1 The absorption, acetylation and excretion of M & B 693, H E Stokinger (by invitation), 2 New York Hospital and Bellevue Hospital, Norman Plummer, Herbert Ensworth (by invitation), 3 Rockefeller Institute, Colin MacLeod (by invitation), 4 Presbyterian Hospital, C A Ragan, Jr, Crispin Cooke (by invitation), 5 Roosevelt Hospital, E B Sanford (by invitation), Discussion by A R Dochez, J G M Bullowa

JANUARY 18—*Genito-Urinary Surgery* Reading of the minutes ¶ Case reports —a] Malignant hiccup as a complication of prostatic resection and cured by bilateral phrenicectomy, Meredith F Campbell, b] Prostatectomy at age of one hundred and ten, J Bayard Clark, c] Leiomyoma of the prostate with resume of twenty cases, Morris Robert Keen (by invitation) ¶ Paper of the evening—Transurethral prostatic resection Experience with 1,200 patients seventy years of age or more, Gershom I Thompson, Rochester, Minnesota (by invitation), Discussion by Henry G Bulbee and J Sturdivant Peard

JANUARY 18—*Otolaryngology* Reading of the minutes ¶ Papers of the evening—Head trauma diagnosis and treatment —a] Fractures involving the nose and face J D Whitham (by invitation) Discussion by Joseph D Kelly b] Fractures of the skull involving the facial bones J Winston Foville Discussion by Isidore Frierer c] Otitis

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## LECTURES ON OBSTETRICS

UNDER THE JOINT SPONSORSHIP OF

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Thaddeus L. Montgomery, Philadelphia

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Joseph N. Nathanson

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*Principles of hormone diagnosis and theories of endocrine therapy  
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Howard C. Taylor, Jr

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*Management of pregnancy complicated by*

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J. Burns Amberson, Jr

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Edwin P. Maynard, Jr

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*Recognition and management of abnormal presentations*

Albert H. Aldridge

April 5

*Sulfamylamide and other therapy in the treatment of post-abort  
sepsis, post-partum sepsis and pyelitis*

Edward G. Waters, Jersey City

BULLETIN OF THE NEW YORK  
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BULLETIN OF  
THE NEW YORK ACADEMY  
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APRIL 1939

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DIAGNOSTIC SIGNIFICANCE OF CHANGES  
IN LEUKOCYTES\*

M M WINTROBE

**B**EFORE discussing leukocytes from the diagnostic view point it will be profitable to consider some of their characters and functions. Because we are accustomed to study these cells after they have been fixed and stained, we visualize them as rounded structures with blue nuclei of various shapes, and cytoplasm of different colors and often containing granules. It is important for our understanding of them, to remind ourselves that the leukocytes are colorless corpuscles which are actively motile. The Lewises<sup>1</sup> have made motion pictures of leukocytes as they grow in small hanging drop cultures in autoplasm. Photographs are taken at the rate of twenty-four frames a minute, and when these are shown at the customary rate of 960 a minute the picture is a most interesting one.

The polymorphonuclear neutrophilic leukocytes are very active cells which rarely cease moving if temperature conditions are those of the body. Locomotion is ameboid in type with long pseudopods extending forward and the nucleus trailing behind. They move at the rate of 26 to 56 $\mu$  per minute. The granules can be seen as tiny round retractile bodies completely filling the cytoplasm and streaming along in it.

Less mature cells of this series are less active. Myelocytes are usually slow-moving in comparison with the polymorphonuclear cells and only in the metamyelocyte or juvenile stage of this series of cells does streaming of the granules, so characteristic of the mature forms, begin to appear. These granules, and the fluidity of the cytoplasm, speak for the functional activity of the cells.

The neutrophilic polymorphonuclear leukocytes are spoken of as microphages because they engulf and digest bacteria and small particles.<sup>2</sup> They form the second line of defense against invading organisms, after the first line, represented by the skin and mucous membranes, has been passed. They probably also play a role in the disposal of necrotic tissue and the removal of inflammatory fibrin. This is done with the aid of enzymes contained in these cells which include proteolytic enzyme,<sup>3</sup> amylase,<sup>4</sup> catalase, trypsin and oxydase.

Eosinophils are less persistently motile than neutrophils. Our conception of the function of these cells is based largely on indirect evidence and depends on the circumstances and situations in which they are found. An important role in detoxification is attributed to them, as well as in the disintegration and removal of protein, of endogenous as well as of exogenous origin.

Lymphocytes move as quickly as polymorphonuclear leukocytes and in a characteristic manner. The nucleus is at the anterior end and the cytoplasm seems to pass through "constriction rings" which appear to be static, that is, they retain their position in relation to objects external to the cell. Lymphocytes are not incessant in their movement but rest from time to time.

The lymphocyte is a mysterious cell from the functional standpoint. It is not phagocytic but seems to be involved in some way in the healing process. Lipolytic enzymes<sup>5</sup> have been found in these cells and have therefore been attributed a role in the metabolism<sup>6</sup> of fat and in the defense against antigens containing lipoids. Because of their strategic position in lymph nodes, lymphocytes have been thought to have an important role in toxin fixation. They may also be concerned in antibody formation.

Monocytes also have a characteristic type of movement. They possess a delicate surface film which is irregular or wavy in outline and the cell advances by a sort of sliding, waving motion. Monocytes contain granules and vacuoles and are actively phagocytic. Because of their liking for large particles, such as protozoa, particulate matter and red corpuscles, they are

known as macrophages and scavengers. From these cells are thought to be derived the epithelioid cell of tuberculosis, the Langhans' giant cell and the tissue macrophage or clasmatocyte (histocyte), cells which are probably important in the defense against bodies too large to be engulfed by monocytes.

The simplest method for studying leukocytes is by the examination of the wet, unstained film of blood. A drop of blood is picked up on a cover-slip. This is inverted on a slide and ringed with vaseline in order to prevent drying. The supravital technique<sup>7</sup> is a modification of this procedure in which certain dyes are added to the blood with the result that granules, vacuoles and mitochondria in the leukocytes are stained and the examination of the living cells is thus facilitated. The method is quite simple and does not deserve the awe in which it has been held.

For routine work, the staining of dried films of blood by one of the Romanowsky procedures, of which Wright's stain is the most popular in this country, is probably the most suitable. This method offers not only permanent preparations which may be easily transported, if necessary, but also stains the nuclei of the leukocytes, an important aid in the differentiation of the various types of cells.

#### CLASSIFICATION OF LEUKOCYTES

The use of stains for the differentiation of leukocytes is based on the brilliant investigations of Paul Ehrlich almost sixty years ago. His studies made possible the distinction of eosinophilic, basophilic and neutrophilic granules and the separation of lymphocytes and monocytes or "transitionals" as he called them, from the myeloid series of cells.

Attempts to subdivide the leukocytes further have been confined chiefly to the myeloid series of cells. In 1904 Arnet<sup>8</sup> attempted to classify the circulating neutrophilic leukocytes according to the morphology of the nucleus. He subdivided these cells into five main groups according to whether the nucleus consisted of one, two, three, four, five or more segments and then further subdivided them as shown in Fig. 1. Such a classification was obviously too complicated and impractical. Nevertheless, the principle of his method is still used today. Arnet showed that the nucleus of the neutrophil in its development from the myelocyte of the bone marrow, becomes gradually more indented and divides, as it grows, into an increasing number of separate lobes. He also introduced the term "shift to the left" to indicate an increase in the young cells and




KERNTEILE				
1	2	3	4	5
M	2K	3K	4K	5K
 0%	0.3%	2.3%	3.8%	1%
W	2S	3S	4S	4KIS
 0.2%	23.5%	5.6%	0.07%	0.4%
T	1KIS	2KIS	3KIS	3K2S
 5%	11.7%	16.7%	6.4%	0.4%
		1K2S	3SIK	4K2S
		16.4%	1.6%	0.07%
			2K2S	3K3S
			4.7%	0.07%
<b>TOTAL</b> 5.2%	35.5%	41.0%	16.6%	1.9%

Fig 1—Arneth's classification of neutrophilic leukocytes. The number of each of these cell types which he considered normal is shown in per cent.

"shift to the right" to indicate an increase in the older cells. These terms arose from the fact that Arneth recorded the number of cells of each type in a series extending from the youngest forms at the extreme left to the oldest forms at the extreme right, in the same order as shown in Fig 1.

The first practical modification of the Arneth method was the Schilling classification (1911). Schilling divided the neutrophils into four groups, namely (1) myelocytes, (2) juvenile neutrophils in which the nucleus is indented but not yet segmented, (3) segmented neutrophils, (4) "stabkernige" or staff forms in which the nucleus is T, V or U shaped, and unsegmented.

The stab cells are characterized by a narrow, irregular and deeply stained nucleus showing little structural detail. The characteristic differentiation of basi- and oxychromatin is absent. Such cells Schilling considers to be produced through a failure of normal maturation. He introduced the terms "regenerative shift to the left" and "degenerative shift to the left." By the former he means an increase in the proportion of young forms of neutrophils which are, however, quite normal in appearance.

and are thought to be sent out from the marrow in response to an urgent demand "Degenerative shift" refers to the presence of many stab cells and indicates the failure of young cells to mature as a result of depression of marrow function due to toxins

In the Schilling hemogram the above mentioned types of neutrophils are classified and eosinophils, basophils, lymphocytes and monocytes are differentiated. Of these cells the juvenile neutrophils make up only 0.0 to 1 per cent and the stab cells 3 to 5 per cent.

At this point may be mentioned an anomaly of neutrophilic leukocytes which has recently attracted attention.<sup>9</sup> Pelger reported finding in the blood of several members of a family in Holland a great number of cells resembling juvenile or stab types of neutrophils although these persons were apparently in good health. Others have since described similar findings in members of other families and this has now come to be regarded as a rare familial anomaly of neutrophils which must be distinguished from the "shift to the left" which occurs in infections.

Innumerable other modifications of the Arneth procedure have been advocated. One of these, namely, that of Cooke and Ponder<sup>10</sup> separates neutrophils into five classes according to the number of lobes. This is certainly a great simplification but it is of relatively little practical value because emphasis is placed on distinguishing polymorphonuclear leukocytes with two, three, four and five lobes. Experience has shown that such a differentiation is of relatively little importance in clinical work. Chief attention should be given to the differentiation of the younger types of neutrophils.

Other modifications of the Arneth procedure have arisen from an attempt to facilitate the differentiation of the segmented and unsegmented forms. Everyone who has tried to make a detailed differential count is aware of the difficulty of deciding whether certain cells should be placed in the unsegmented or the segmented group. The so-called filament, non-filament count was proposed in an attempt to simplify this task. If a fine thread of chromatin can be distinguished as joining two or more lobes, the cell is classified as filamented whereas one which shows no such thread, even though the shape of the cell nucleus is so irregular that it suggests lobulation, is classed as nonfilamented. The nonfilamented cells are said to make up 5 to 16 per cent of the leukocytes.

The chief objection to the filament-nonfilament count is that it is too arbitrary. While perhaps for some technicians a simple procedure

FIG 2

## HARKIN'S TOXIC INDEX

$$T I = \frac{10 M_j + 5 J + 2 (S - 10)}{10 E + 2 L + A}$$

*Legend*  $M_j$  = myelocytes,  $J$  = juveniles,  $S$  = staff forms,  $E$  = eosinophils,  
 $L$  = lymphocytes,  $A$  = adult polymorphonuclears

such as this is essential, it seems a better plan to scrutinize doubtful cells carefully and attempt to decide whether they are truly segmented or not

It would serve no useful purpose to enumerate the various other hemograms, indexes and formulae which have been proposed for use in the study of the leukocytes. To mention some of their names will give you some idea of their nature. Walker's index of resistance, the weighted mean of Cooke and Ponder, Needle's neutrophilic graph, Boerner's nuclear index, and so on. Harkin's toxic index<sup>11</sup> will give you some idea of the extremes to which this desire for a formula has led (Fig 2). These devices represent an attempt to give mathematical precision to a biologic process which does not lend itself readily to mathematics. They introduce no new morphologic criteria but, instead, enshroud a relatively simple subject with an air of complexity and mysticism.

A discussion of the neutrophilic leukocytes would be incomplete if attention were not called to the significance of qualitative changes in the cytoplasm of neutrophils<sup>12,13</sup>. In the presence of severe infections, some of the granules of the neutrophils which normally are small, uniform in size, pink in color, and regularly dispersed, stain more deeply. These basophilic granules, as they are called, may be small and distributed among the normal pinkish granules, or they may be quite large, few in number, and no normal granules may be seen. Abnormality of the cytoplasmic structures of the neutrophils is also indicated in such cases by the appearance of the cells after staining by the peroxidase method. Normally, neutrophilic cells are full of oxidase staining granules. When basophilic granulation is demonstrable by one of the Romanowsky staining methods, few oxidase reacting granules are found in the cells.

The toxic granules may be present in either young, immature cells or in the mature, segmented forms. In addition to these changes, evidence

of cell damage may be found in neutrophils in the form of bluish staining or vacuolization of the cytoplasm. In rare instances one may see neutrophils entirely lacking in specific granules.<sup>14</sup>

It is, of course, of extreme importance to prepare and stain blood slides carefully when the morphologic differences above mentioned are sought. For differential blood counts, thin films of blood on cover glasses give much better preparations than smears made on slides. It is important to avoid over-staining and it is wise to make control preparations of normal blood, stained in the same way as the preparations of the patient's blood. Before assuming that a given preparation shows "toxic" granules and "stabkernige," one must be sure that similar changes are not observed in normal blood, similarly stained. If the blood film is made on a slide, it is a good plan to make a film of normal blood at one end of the slide and a film from the patient's blood at the other. The whole slide can then be stained at the same time.

It was stated above that in the differential examination of the neutrophils, emphasis should be placed on the younger forms rather than on the multi-segmented types. There is one type of cell to which reference should be made, however. This is a polymorphonuclear leukocyte which is unusually large and which possesses a nucleus of six to ten lobes. This type of cell is sometimes called a macropolycyte and is characteristically seen in the blood of cases of pernicious anemia. It is rarely seen in other conditions.

It has not been shown conclusively that a maturation cycle can be distinguished among the lymphocytes of the blood such as occurs in the myeloid series. Lymphocytes have been classified as large and small, usually on the assumption that the former are the less mature cells. However, there is no adequate evidence that the size of lymphocytes is a criterion of their age.<sup>15</sup> Wiseman<sup>16</sup> has recently recommended the differentiation of lymphocytes as young, mature and old on the basis of differences in the degree of basophilia of their cytoplasm, number of mitochondria and degree of pyknosis of the nucleus and has reported significant alterations in the Y : M : O ratio in tuberculous infection particularly. In practice, Wiseman's differentiation of the lymphocytes is difficult even if it is admitted that it is theoretically sound—something which not all hematologists are ready to do.

In summary, then, a simple and practical classification of the leukocytes normally occurring in the blood is one which distinguishes the three



TABLE I  
RELATIVE AND ABSOLUTE VALUES FOR LEUKOCYTE COUNTS  
IN NORMAL ADULTS PER CMM BLOOD

<i>Type of Cell</i>	<i>Per cent</i>	<i>Absolute Number</i>		
		<i>Average</i>	<i>Minimum</i>	<i>Maximum</i>
Total leukocytes		7,000	5,000	10,000
Myelocytes	0	0	0	0
Juvenile neutrophils	3-5	300	150	400
Segmented neutrophils	54-62	4,000	3,000	5,800
Eosinophils	1-3	200	50	250
Basophils	0 -0.75	25	15	50
Lymphocytes	25-33	2,100	1,500	3,000
Monocytes	3-7	375	285	500

classes of leukocytes, namely, lymphocytes, monocytes and granulocytes, and subdivides the latter not only according to the type of granulation but according to the age of the cells, namely, juvenile forms and segmented forms (Table 1) In addition, attention should be given to so-called "toxic" changes in the nuclei and cytoplasm of these cells

Further consideration cannot be given here to the subject of the morphological characteristics of the leukocytes It may be stressed, however, that in learning to differentiate these cells one should acquire the habit of systematically examining the whole cell One should note the size and shape of the nucleus, the nature of the chromatin, the presence or absence of a nuclear membrane, a perinuclear clear zone, and nucleoli, as well as the color of the cytoplasm, the size, color and number of granules within it and the presence of any unusual structures By so doing, one will acquire the habit of seeing all one looks at and in time cells will be distinguished quickly because of an automatic recognition of these differences The actual identification of cells regarding which there is some doubt can be made only by weighing the evidence for and against each type of cell considered

#### TECHNICAL ERROR AND PHYSIOLOGIC VARIATIONS

Before discussing the changes which occur in leukocytes in disease, we must consider the variations which may be attributed to technical error as well as the fluctuations which occur under physiologic conditions

By the term "technical error" we refer to the errors unavoidably associated with the methods employed rather than those attributable to the defective technique of the examiner. The latter, of course, may be very great and has sometimes led to grave errors in diagnosis.

It is generally agreed by those who have investigated the subject, that the apparatus of responsible manufacturers in the hands of experienced workers introduces almost negligible variations as the result of filling the sampling pipet, dilution of the sample, variations in the calibration of the appliances, and the personal factor of counting. The chief error occurs in the mixing of the cells and diluting fluid, filling the counting chamber by capillarity and settling of cells by chance on the ruled field of the counting chamber.<sup>17</sup> The mean error due to these causes amounts to possibly as much as 600 cells when the leukocyte count is normal (7000) and an area of only 4 square millimeters (one chamber) is counted, or about 425 cells if the count is made in two chambers ( $e = \sqrt{N}$ , when  $e$  is the mean error and  $N$  is the number of cells counted<sup>18</sup>). When the leukocyte count is, say 16,000, the probable error would be about 900 if the count were made in one chamber only. Thus for these two levels of leukocyte count one should consider ranges of 6400 to 7600, and 15,100 to 16,900, respectively, as within the range of error of distribution.

Another question of great importance in the interpretation of the leukocyte count, is the significance of a change in the percentage of cells, let us say from 70 per cent polymorphonuclears to 80 per cent. Again assuming that the differential count has been done carefully on well stained preparations, two factors must be considered. One is the manner of preparation of the blood film, whether on cover-slips or on slides. It is generally agreed that in smears drawn or pulled on slides, the larger leukocytes tend to accumulate at the margins while the smaller cells are distributed in the central portion of the film. If it is not possible to make cover-slip preparations, a zig-zag course about the edge of the slide-smear should be followed.

The second source of error is one of chance distribution. This error is reduced as the number of cells examined is increased. Statistical studies show that a minimum of 200 cells should be counted.<sup>18</sup> The error is considerably less when this number of cells is counted than when only 100 cells are enumerated. Goldner and Mann<sup>19</sup> have published "confidence curves" from which one may estimate the probable error of a differential count when 200 cells are counted. According to these curves

one may, 19 times out of 20, expect the true proportion of polymorphonuclears to be somewhere between 63.6 and 76.4 per cent when the count is found to be 70 per cent. Accordingly, a count of 80 per cent on the same patient at another time could probably be considered as being significantly increased. However, if the count were made on only 100 leukocytes, the difference would be scarcely significant.

I should like to lay some emphasis on the subject of error in leukocyte counting, because in general physicians are not sufficiently critical of this, as of many other laboratory procedures. Because the results are expressed numerically, many derive a false sense of accuracy from them. It is important to scrutinize the figures as carefully as one examines the patient. In fact, it is probably even more important to do so because the physician usually examines the patient himself whereas the laboratory studies are often left to an assistant.

Another matter of some importance is the physiologic variation of the leukocyte count.<sup>20</sup> It is generally stated that the normal range of the leukocyte count is 5000 to 10,000. It is not sufficiently recognized that in 11 per cent of apparently normal persons values above 10,000 are found.<sup>21</sup> Then again, in some persons the leukocyte count is normally well below 10,000 and this figure in them represents a pathological leukocytosis. Furthermore, the state of physical and mental rest influences the leukocyte count and fluctuations normally occur during a single day as well as from day to day. Under conditions of complete mental and physical rest a basal level of 5000 to 7000 cells is usually attained. The random activity of ordinary routine is often associated with a moderate increase and higher levels are found in the afternoon than in the morning. Digestion of food probably does not cause appreciable leukocytosis as was formerly the opinion.

Strenuous exercise or convulsive seizures cause a well marked leukocytosis, even as high as 35,000. It is important for the physician to bear in mind, moreover, that fear and apprehension, pain and even nausea and vomiting may produce leukocytosis. The injection of adrenalin and ether anesthesia do the same. It is important to note, however, that the leukocytosis produced by these factors is not characterized by an increase in young cells in the blood. Consequently a differential leukocyte count is of great importance in distinguishing physiologic from pathologic leukocytosis.

TABLE II

FACTORS INFLUENCING THE MAGNITUDE OF NEUTROPHILIA

- 1 The cause of the neutrophilia pyogenic, especially coccal vs typhoid or tubercle bacilli
- 2 Localization of the process then even tubercle bacilli may cause neutrophilia
- 3 Virulence of the organism, reactivity of the patient

Numerical increase = resistance of the individual  
 Percentage increase }  
 Toxic Changes        } = effort of the response

TABLE III

CAUSES OF NEUTROPHILIA

- 1 Acute infections, especially coccal  
     *Certain bacteria fungi, spirochetes, viruses and parasites*  
 Localized infections  
     *Certain general infections, such as rheumatic fever, diphtheria, smallpox*  
     *Development of complications in diseases usually not associated with neutrophilia*
- 2 Intoxications  
     (A) Metabolic uremia, diabetic acidosis, eclampsia, gout  
     (B) Poisoning by chemicals and drugs, lead, mercury, digitalis, adrenalin  
         *Insect venoms, black widow spider*  
         *Foreign proteins, after a preliminary leukopenia*
- 3 Acute hemorrhage
- 4 Postoperative
- 5 Non-inflammatory conditions, such as coronary thrombosis
- 6 Malignant neoplasms when growing rapidly, especially in G-I tract, liver, bone marrow
- 7 Sudden hemolysis of red corpuscles
- 8 Physiological in the newborn, during labor, after strenuous exercise, after repeated vomiting, convulsions, paroxysmal tachycardia
- 9 Myeloid leukemia and erythremia

TABLE IV

CAUSES OF LEUKOPENIA

- 1 Certain infections  
     (A) Bacterial, e.g., typhoid, paratyphoid, undulant fever  
     (B) Infections caused by viruses, e.g., influenza, measles, rubella  
     (C) Protozoal infections, e.g., malaria, relapsing fever, kala-azar
- 2 All types of overwhelming infections, e.g., military tuberculosis, septicemia, and cachectic and debilitated states and inanition
- 3 Certain conditions of unknown causation e.g., catarrhal jaundice, cirrhosis of the liver, Felty's syndrome, lupus erythematoses disseminatus
- 4 Hemopoietic disorders, especially those involving the spleen, Banti's disease, Gaucher's disease, also in pernicious anemia (relapse), chronic hypochromic anemia, aplastic anemia, myelophthisic anemia, idiopathic granulocytopenia
- 5 As the effect of recognized toxic agents  
     Chemical, e.g., benzol, arsenic, lead, bismuth, mercury, antimony, amidopyrine  
     Physical, e.g., radioactive substances
- 6 In anaphylactoid shock and in early stages of reaction to foreign protein

## VARIATIONS OF LEUKOCYTES IN DISEASE

It is unnecessary to enumerate in detail all of the conditions in which various types of leukocytic reaction occur. However, some of the general principles which underly these changes may be considered with advantage.

Leukocytosis is usually due to an increase in the number of cells of the neutrophilic series. We shall refer to this type of leukocytosis as neutrophilia for the sake of clarity.

Three factors influence the magnitude of neutrophilia (Table II). These are (1) the cause, (2) the localization of the process, and (3) the virulence of the invading organism, the reaction of the patient and his general resistance. In general, pyogenic and particularly coccal bacteria call forth a neutrophilic response, whereas other bacteria such as typhoid and the tubercle bacillus have no such effect. However, a generalized infection, even when it is the result of the invasion of cocci, is often not associated with an increase in the total leukocyte count. So important is the factor of localization that if the infection is delimited, neutrophilia may result even when the invading organism is one which usually is associated with leukopenia. Tuberculous meningitis is an example of this. Finally, with reference to the third factor, it is generally appreciated that when an infection is mild, neutrophilia may be absent and when it is overwhelming and the person involved too feeble to resist, neutrophilia may not occur. In general, the total numerical increase in neutrophils may be regarded as indicating the resistance of the individual to an infection while the percentage increase of these cells and the qualitative changes indicate the effort of the response and the severity of the infection. Thus in the presence of an overwhelming infection, the total leukocyte count may not be increased, but there is a marked "shift to the left," the nuclei of many of the juvenile neutrophils are pyknotic and toxic granulation is found in their cytoplasm.

The causes of neutrophilia have been summarized in Table III. The causes of leukopenia are listed in Table IV.

At this point reference may be made to what is known as the "leukopenic index." This refers to leukopenia which is said to occur in allergic individuals following the ingestion of food to which they are sensitive. When carried out under certain conditions as described for the test, a decrease in the leukocyte count of 1000 or more cells per c mm. is inter-

TABLE V

CAUSES OF EOSINOPHILIA

- 1 Allergic disorders: bronchial asthma, urticaria, angioneurotic edema, hay fever
- 2 Skin diseases: especially pemphigus and dermatitis herpetiformis
- 3 Parasitic infestations: especially parasites which invade the tissues: e.g., trichinosis, echinococcus disease, less regularly in intestinal parasitism
- 4 Certain infections: e.g., scarlet fever, chorea, erythema multiforme
- 5 Certain diseases of the hemopoietic system: chronic myeloid leukemia, erythremia, Hodgkin's disease, after splenectomy, pernicious anemia
- 6 Miscellaneous disorders: periarthritis nodosa, tumors of the ovary or those involving serous surfaces or bones: certain types of lung infiltration
- 7 As a familial abnormality

TABLE VI

CAUSES OF LYMPHOCYTOSIS

- 1 Certain acute infections: pertussis  
infectious mononucleosis
- 2 During subsidence of acute infection and recovery phase of granulocytopenia
- 3 Many protozoal infections: malaria, Rocky mountain spotted fever, kala-azar, trypan-  
somnia, fever
- 4 During the stage of convalescence from an acute infection
- 5 Exophthalmic goitre (usually only relative lymphocytosis)
- 6 Infants and young children, especially in the presence of rickets and malnutrition
- 7 Lymphatic leukemia

TABLE VII

CAUSES OF MONOCYTOSIS

- 1 Certain bacterial infections: tuberculosis, subacute bacterial endocarditis, brucel-  
losis, typhus, rarely in typhoid
- 2 During subsidence of acute infection and recovery phase of granulocytopenia
- 3 Many protozoal infections: malaria, Rocky mountain spotted fever, kala-azar, trypan-  
somnia, oriental sore
- 4 Hodgkin's disease, also in diseases of disturbed lipid metabolism, such as Gaucher's  
disease
- 5 Monocytic leukemia
- 6 Tetrachlorethane poisoning

preted as indicating incompatibility of food. This method has also been proposed as a means of detecting other forms of allergy. In the light of what has already been said regarding the unavoidable error in leukocyte counting, it is no wonder that this test has been the subject of considerable criticism.<sup>22</sup> Nevertheless, it has its ardent advocates.

The causes of eosinophilia are listed in Table V. It is noteworthy that whereas eosinophilia occurs as a characteristic of a small number of infections,<sup>23</sup> in general eosinophils disappear when neutrophilia occurs. This phenomenon has been called "Simon's septic factor." Recovery in such cases is often marked by eosinophilia.

The basophilic leukocytes are found increased in chronic myeloid leukemia and in erythremia, and sometimes in chronic hemolytic anemia, in chlorosis, following splenectomy, in Hodgkin's disease, in smallpox and in chickenpox and following the injection of a foreign protein, as well as in chronic inflammation of the accessory sinuses.

The causes of lymphocytosis are enumerated in Table VI. This refers to absolute lymphocytosis. Relative lymphocytosis occurs in most of the conditions associated with neutropenia.

Plasma cells are rarely found in the circulating blood. They have been noted in rubella, in scarlatina and in measles.<sup>24</sup>

The causes of monocytosis are listed in Table VII. The role of the monocyte in tuberculosis has attracted intensive study and it has been shown that this cell takes an important part in the cellular reaction to the tubercle bacillus. The lipoids of this organism are phagocytized by monocytes, are partially degraded within them and cause their transformation to epithelioid cells. This activity is reflected in the circulating blood and it is now generally accepted that monocytosis in a tuberculous patient is an unfavorable sign. Increasing reliance is being placed on the ratio of monocytes to lymphocytes, for the latter vary inversely with the former in this disease, and lymphocytosis occurs when the tuberculous lesion is healing. Normally there is one monocyte to at least three lymphocytes. In tuberculous infections, a favorable M/L ratio is 1/3.6, while a ratio of 1/0.8 is a very unfavorable one. At the same time the proportion of young lymphocytes decreases, a phenomenon which Wiseman<sup>25</sup> has named "curve of degeneration." Improvement in tuberculosis, he has found, is associated not only with a fall in the number of monocytes, but an increase in the number of young lymphocytes ("curve of regeneration"), and in the total number of lymphocytes. These

changes in the leukocytic picture may appear some time prior to other indications of the change in the status of the patient, and thus are of great prognostic value

### PROGNOSTIC VALUE OF THE LEUKOCYTIC PICTURE

Study of the leukocytes is clearly of value as an aid in diagnosis. A painstaking differential count may be particularly helpful in discovering cryptic infections of subacute or chronic types in which there is no increase in the total leukocyte count. When several counts have been made, the leukocyte picture may be a useful aid in estimating prognosis. In Table VIII various factors which are of importance in the estimation of prognosis on the basis of the leukocyte count are listed. All of these have already been referred to and only certain principles need now be mentioned.

Generally three phases may be observed in the leukocytic reaction to an infection.<sup>26</sup> During the progressive stage, neutrophilia predominates and the severity of the infection as well as the reaction of the patient may be gauged by the magnitude of the leukocyte count, the degree of "shift to the left" and the presence of toxic cytoplasmic granulation. Thus, a slight neutrophilia with slight nuclear "shift" suggests a mild infection, whereas a moderate leukocytosis with moderate "shift" (say, 16 per cent of young forms), together with disappearance of eosinophils and decrease of lymphocytes, signifies a moderately severe infection. As already stated, still more marked leukocytosis or a fall in the leukocyte count, with an even greater "shift to the left" than before, are grave signals. Unfavorable signs in the leukocyte picture are listed in Table IX.

Except in certain diseases, such as tuberculosis, in which an increase in the number of monocytes is an unfavorable sign, the reappearance of these cells in the course of an acute infection usually indicates the beginning of the recovery stage. Their return is often followed by the reappearance of eosinophils. Finally, lymphocytosis develops during the period of convalescence. The changes in the blood picture during recovery are shown in Table X.

By a consideration of the details of the leukocyte count, then, and particularly by noting the changes which occur from day to day, a valuable estimate of the course of the patient's illness can be made, sometimes before other signs are manifest.



TABLE VIII

ESTIMATION OF PROGNOSIS FROM THE LEUCOCYTIC COUNT  
SIGNIFICANT FACTORS

- 1 Magnitude of leukocyte count
- 2 Proportion of immature cells
- 3 Number of "toxic" forms of leukocytes
- 4 Degree of reduction in number of eosinophils
- 5 Degree of reduction in number of lymphocytes
- 6 Degree of increase in monocytes (tuberculosis)

TABLE IX

## UNFAVORABLE SIGNS IN THE LEUCOCYTIC PICTURE

- 1 Extremely high total number of leukocytes with high percentage of neutrophils or
- 2 Failure to develop leukocytosis
- 3 High proportion of immature cells especially if they outnumber mature forms
- 4 Absence of eosinophils
- 5 Marked absolute reduction of lymphocytes
- 6 Presence of numerous toxic, degenerative forms

TABLE X

## CHANGES IN BLOOD PICTURE DURING RECOVERY

- 1 Falling total leukocyte count with diminishing proportion of neutrophils
- 2 Decrease of immature forms
- 3 Temporary increase of monocytes
- 4 Reappearance or increase of eosinophils
- 5 Increase in number of lymphocytes
- 6 Absence or decrease of toxic forms

TABLE XI

## LEUKEMOID BLOOD PICTURE

- 1 Infections, presenting pictures resembling  
myeloid leukemia, pneumonia, meningococcus meningitis, diphtheria, tuberculosis,  
lymphoid leukemia, whooping cough, chickenpox, infectious mononucleosis
- 2 Intoxications, eclampsia, severe burns, mercury poisoning
- 3 Malignancy, especially with bone metastases, also multiple myeloma, myelofibrosis,  
Hodgkin's disease
- 4 Severe hemorrhages, sudden hemolysis of blood

## LEUKEMOID BLOOD PICTURE

In rare instances the leukocytic response to disease may be so marked or of such a character that the blood picture resembles that seen in one of the types of leukemia. These have been termed leukemoid blood pictures and a number of such reports are found in the literature. In some instances it has only been the magnitude of the leukocytic reaction or its unusual quality which suggested leukemia. In many cases, however, severe anemia accompanied the leukocytic change and even nucleated red corpuscles of various types were found. In some instances even the clinical picture, because of fever, hemorrhages, splenomegaly or adenopathy, suggested leukemia. The true diagnosis of some of these cases was evident only on postmortem examination.

In Table XI, conditions in which leukemoid pictures have been observed are listed. In the infections, extremely high leukocyte counts have sometimes been found, even as high as 112,000 in cases of septicemia,<sup>27</sup> 176,000 in whooping cough,<sup>28</sup> 81,200 in chickenpox<sup>29</sup> and 63,000 in infectious mononucleosis. It is in association with tuberculosis, however, that leukemoid pictures have been most frequently described.<sup>30-31</sup> The tuberculosis has usually been miliary in type or it involved the lymph nodes or spleen. The leukocytic picture in such cases has resembled most often that of acute myeloblastic leukemia and leukocyte counts as high as 156,000 have been reported.

In a case of eclampsia a leukocyte count of 100,000 has been recorded, while in an instance of mercury ointment poisoning, 69,500 leukocytes with 24 per cent myelocytes, were found.<sup>32</sup> In a case of Hodgkin's disease, a leukocyte count of 250,000 has been reported.<sup>33</sup>

These examples of leukemoid pictures are, of course, extremely rare. They are mentioned here only to emphasize the importance of taking into consideration the whole clinical picture rather than a single finding in making the diagnosis.

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## PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA\*

NORMAN PLUMMER AND HERBERT ENSWORTH

LESS than a year has passed since the first reports appeared in the English literature, describing the experimental studies on sulfapyridine (M & B 693). The clinical experience with this drug is still very much limited. Nevertheless, most of us working in pneumonia investigation are already willing to concede that this new drug definitely influences the course of the pneumococcus infection and quite probably increases the chances of recovery. The mode of action remains remarkably obscure, and it is too early to be completely assured that serious reactions do not occur.

Sulfapyridine has been used on the medical services of New York Hospital and the First and Second Divisions of Bellevue Hospital during the past three months and it is our privilege to report this experience. During this period, the drug has been administered to 111 patients of whom eighty-eight were diagnosed pneumonia. The drug was given by mouth in all cases. The initial dose was usually 2.0 grams, subsequent doses of 1.0 gram were given every four hours until the desired therapeutic effect had been obtained. Most of the patients in the total series received an average of 16.0 grams. In some the preparation was discontinued after a few grams had been given because of the severe nausea and vomiting produced. In a few cases a much larger total dosage was administered, in one instance 46.0 grams. All of the patients except two were hospitalized, consequently their progress was closely followed by the routine blood counts, urine analyses, and other indicated tests. All of the pneumonias had at least one sputum typing, one blood culture, and all except a very few had one or more chest x-ray examination. A few of the more recent cases have had blood sulfapyridine determinations.

From the start of this investigation of sulfapyridine particular atten-

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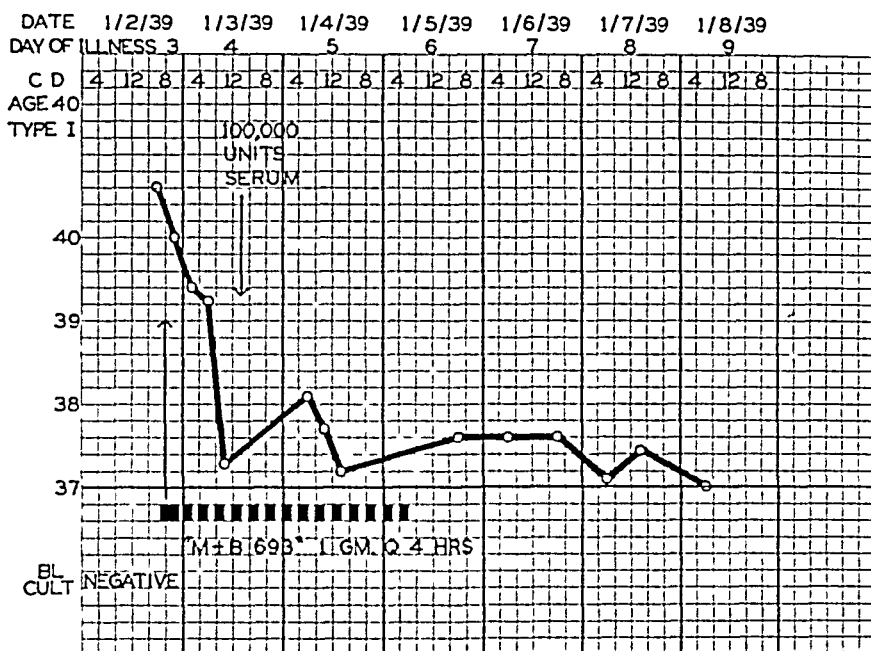


Chart 1—This is the chart of a forty year old woman admitted to Bellevue on the fourth day of illness. Sulfapyridine 2 grams, was given by mouth shortly after admission. The drug was continued at four hour intervals in 1 gram amounts during the next two days. The temperature dropped to nearly normal on the following day after 5 grams of sulfapyridine had been given. The blood culture taken on admission was negative. The sputum typing was not complete until the day after admission when it was reported Type I. Even though the temperature was normal it was thought wise to give 100,000 units of Type I antipneumococcus serum.

tion has been focussed upon the occurrence of untoward effects. In the total series of 111 cases, during the three-month period of this study, we have encountered no serious reaction to the drug in the dosage given. The blood counts have revealed no particular changes in the red or white cells. The urine analyses showed only the occasional trace of albumin which occurs in febrile conditions. A few patients had a mild icterus such as is occasionally seen during the course of pneumonia. In this series, there was no case of toxic hepatitis, neuritis, nephritis, or agranulocytosis, —complications known to occur in pneumonia, but which must be ruled out as possibly being related to the therapeutic agent used.

The principal disadvantage of sulfapyridine is its effect on the gastrointestinal tract. Nausea and vomiting frequently occur, 55 per cent of the patients had nausea and 40 per cent had both nausea and vomiting.

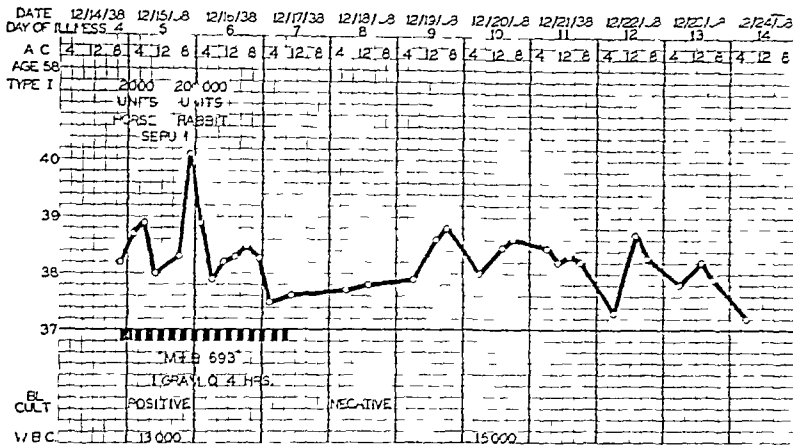


Chart 2—A fifty-eight year old patient with Type I pneumonia and a positive blood culture, treated with sulfapyridine and serum. This therapy controlled the toxemia and septicemia. On the day after admission to the hospital, there were physical and x-ray signs of fluid, which on thoracentesis was found to be a thin exudate, culturing Type I pneumococci. The fluid was quickly absorbed and surgery has not been necessary, although the convalescence has been considerably retarded.

In about 10 per cent of the cases it was necessary to discontinue the therapy because of the severity of these symptoms. The question has arisen whether the gastric irritability is of local or central origin. The fact that the chemical when chewed in the mouth is so bland and innocuous, together with the finding that nausea usually does not occur until after four to six grams have been given, seems evidence in favor of the central origin. Blood determinations should aid in answering this problem.

We come now to the important question: What is the value of sulfapyridine in the treatment of pneumonia? The series which we have for analysis includes eighty-eight patients having definite signs of pneumonia, in whom chronic pulmonary disease has been excluded by the course and bacteriological findings. We have included both the typical and atypical acute pneumonias, also cases in which the pneumonia occurred as a complication of serious systemic disease. Patients who died shortly after admission to the hospital have also been included. We have carefully excluded cases of influenza and acute bronchitis. Twenty of the eighty-eight patients received specific antipneumococcus serum in addition to sulfapyridine.

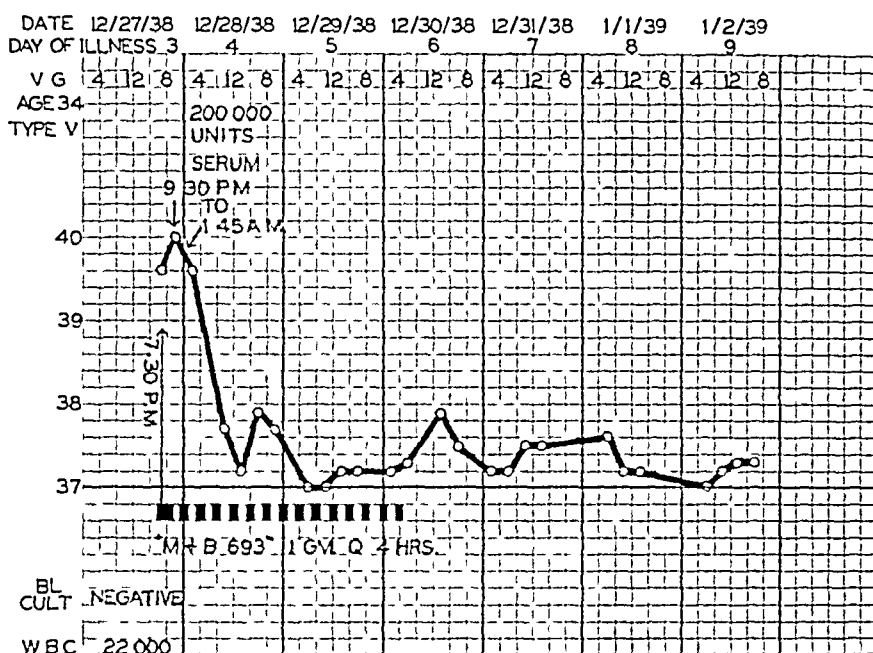


Chart 3—A thirty-four year old man admitted on the third day. On admission, the sputum showed Type V pneumococci, the blood culture was negative, and the white blood cell count was 22,000. Both sulfapyridine and serum were given with a quick and positive response.

The mortality rate in this series of eighty-eight cases is 8 per cent,\*\* seven of the patients having died. This is an extremely low figure when compared with an expected fatality rate of from 25 per cent to 35 per cent in similar groups of cases. However, a number of factors must be taken into consideration in estimating the accuracy of this figure. The series is small, the mortality rate in pneumonia is usually lower in the fall and early winter season than in the late winter, there are indications that pneumonia recently has been of a milder form. Also, the series contains more than the average number of pneumonias caused by the higher types and the unclassified pneumococcus, forty-one of the eighty-eight cases falling in this group. The percentage of septic cases is only 6 per cent, which is low. On the other hand, the incidence of systemic disease is high. Also, in the series of eighty-eight patients, nineteen were

\*\* The total series at the time of publication included 157 cases of pneumonia with fifteen deaths, a mortality rate of 9.5 per cent. Thirty-six patients had Type III pneumonia, of which two died a mortality of 5.6 per cent. Forty-eight of the patients were given both serum and sulfapyridine and of this group two died a mortality of 4.1 per cent.

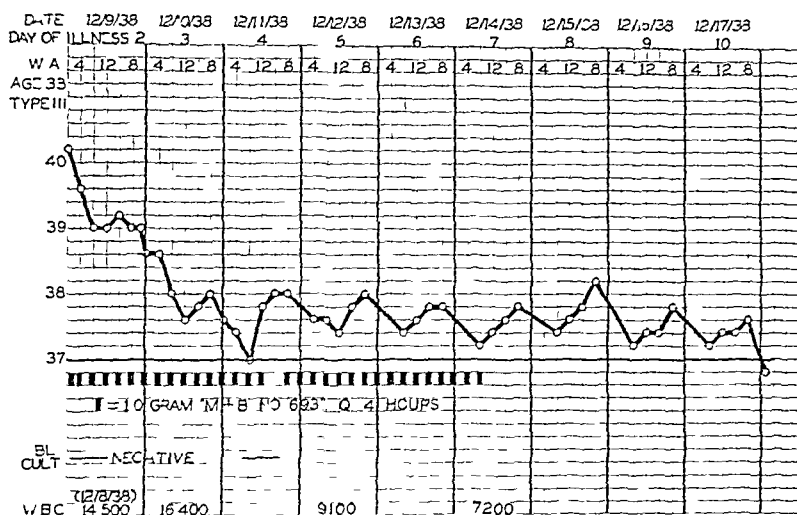


Chart 4—A thirty-three year old woman admitted to New York Hospital, the day following an acute onset. On admission, the sputum showed Type III organisms, the blood culture was negative, and the leukocytes were 14,500. Sulfapyridine was started promptly, and because of extensive pulmonary involvement was continued until 32 grams had been administered. Although the temperature did not drop to normal until the tenth day, the severe toxemia was quickly controlled. The leukocyte count rose from 14,500 to 16,400 after the sulfapyridine was started, and even though 32 grams of the chemical were administered, there was no evidence of agranulocytosis during the hospital stay. This patient had practically no gastrointestinal disturbance from the drug.

over fifty-five years of age, and twenty-four had Type III infection.

The mortality rate in the Type III pneumonia is only 8 per cent, two of the twenty-four cases having died. Three of the Type III cases had positive blood cultures, and two of these recovered. Again there are too few cases from which to make any deductions.

A brief description of the seven fatal cases is important for a fair analysis of our results. Two of the deaths were from Type III infection, one of whom died twelve hours after admission to Bellevue, the blood culture plate showing innumerable Type III colonies, and the patient having received only 6 grams of sulfapyridine. The other Type III fatality was a bad alcoholic, in whom the diagnosis of pneumonia was not made until a few hours before death and to whom only 3 grams of the drug had been administered. The only other patient with a fixed type



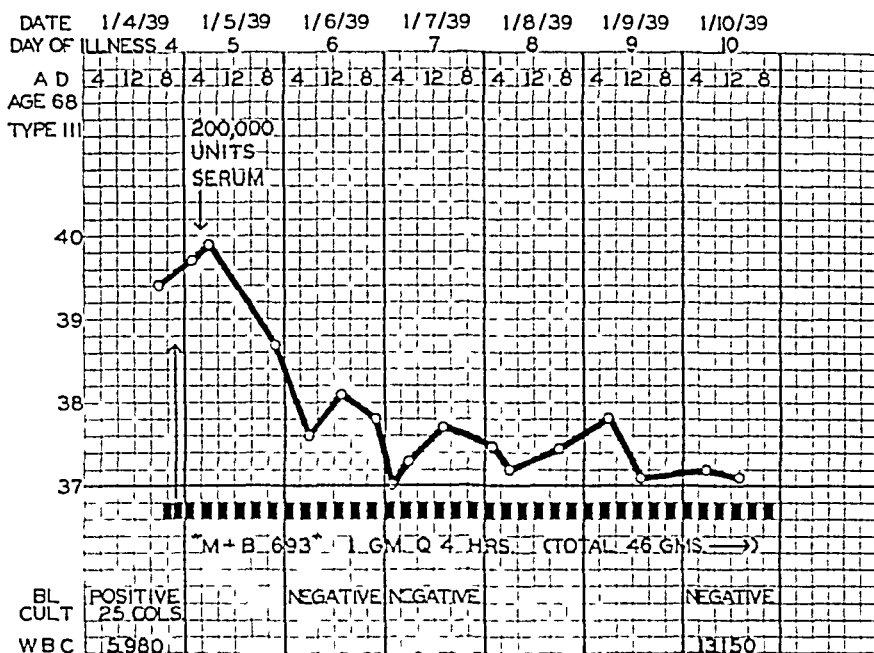


Chart 5—This case alone gives evidence that we now have available, therapeutic agents more effective than any previously used. This sixty-eight year old woman was admitted to Bellevue on the 4th day of a very acute illness. On admission the sputum showed Type III pneumococci and the blood contained 25 Type III organisms per cubic centimeter. The leukocyte count was only 5,980. Sulfapyridine was started as soon as the clinical diagnosis of pneumonia was made. Early on the second day 200,000 units of rabbit serum were injected intravenously. The toxemia and septicemia were quickly controlled. The white blood cell count rose from 5,980 to 13,150 during the period that sulfapyridine was given. Because of the grave prognosis in such a case, the drug was continued until 46 grams had been given. There was no gastric irritation, and no other untoward reaction.

who died, showed a Type IV in the sputum. In this case there was definite response to 17 grams of sulfapyridine, but a few days later, the patient died suddenly after a huge, foul lung abscess had commenced draining. Two patients regarded as having unclassified pneumococcus pneumonia died. One of these was seventy-eight years of age. The other had had pulmonary symptoms for six weeks or more, had been in Bellevue for two weeks and was treated with sulfapyridine just a few days before his death. In both of these cases there is some question as to the true bacteriological diagnosis. The remaining two fatalities occurred in the New York Hospital series. One was a man of sixty-three years, with

arteriosclerotic heart disease and auricular fibrillation who developed an acute pneumonia and was given in all 100 grams of sulfapyridine. There seemed to be satisfactory response to the drug, but two days after it had been discontinued, he suddenly developed severe pain in the chest and died. The other was one of pulmonary infarct and pneumonia following pregnancy. The foul, purulent sputum which the patient had, showed Friedlander's bacilli along with other aerobic and anaerobic organisms. Again the patient showed a temporary response to sulfapyridine, but died later with empyema and other complications. It is evident that the mortality rate would be reduced even further if some of the questionable fatal cases were excluded from the series. The possibility of a relationship between the deaths and the use of sulfapyridine in the patients with coronary disease and lung abscess has been considered but seems remote.

The clinical response to sulfapyridine is as convincing as the reduction in mortality rate. With remarkable regularity the temperature drops to normal within from twenty-four to thirty-six hours after the therapy is instituted. Such a response occurred in forty-five of the eighty-eight cases, and in a number of others the response was a very satisfactory one. The active phase of the disease is considerably shortened, although the signs of consolidation seem to run through their usual cycle. A mild cyanosis occurred in a small percentage of the cases. In no case did the white blood cells drop to a low figure. There were, however, several cases with initial leukopenia, in which the white blood cells returned to a more normal figure following the drug.

Serum therapy (in most cases rabbit serum) was given to twenty of our eighty-eight patients. The results in this group are particularly striking. All of the patients recovered. There was a spectacular drop in temperature in every case. The series included three patients with positive blood cultures, one of whom was a Type III with twenty-five organisms per cubic centimeter on the initial blood culture examination. On the other hand, the serum-treated group included only cases of typical pneumonia. Furthermore, in some of these, as will be demonstrated in the charts, the serum was administered after the temperature was normal.

In summarizing, it should be emphasized again, that this is a preliminary report, and that on such a limited experience no positive conclusions can be drawn. In our results there is some evidence that a combination of sulfapyridine with serum gives greater benefit than either the serum or the chemical alone. But until we can ascertain the relative values

of serum alone, sulfapyridine alone, or a combination of both—our present method of type diagnosis and serum treatment should not be changed. For ourselves and the several people working with us, this recent experience has been most encouraging, and seems to point the way to a more effective treatment of pneumonia.

## PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA\*

HARRISON FITZGERALD FLIPPIN

IT is indeed a great pleasure for me to be here tonight and hear these brilliant presentations on the treatment of pneumonia in New York City. Our group in Philadelphia, which is composed of Dr. John S. Lockwood, Dr. D. Sergeant Pepper, Dr. Leon Swartz, and myself, first became interested in the treatment of pneumonia with sulfapyridine last August. Our interest in this chemotherapeutic agent was stimulated by the investigative work of one of us, Dr. John S. Lockwood, on the action of sulfanilamide, which has gained considerable recognition, and secondly, our interest was stimulated by the work of Gaisford and Evans in England, who have reported 200 cases of pneumonia treated alternately with sulfapyridine. Of the 100 cases treated with sulfapyridine the mortality rate was 8 per cent as compared with 27 per cent in the control series, which received other forms of therapy. Naturally when a new therapeutic agent, especially a chemotherapeutic agent, is presented for the treatment of pneumonia, and particularly in the city of Philadelphia, it meets with a great deal of opposition. I am happy to say, however, that sulfapyridine has been enthusiastically received by a number of the Philadelphia physicians.

Tonight I would like to present the first 100 cases (Table I) of pneumonia which we have treated in Philadelphia with sulfapyridine since last August. Of this group we were able to detect the pneumococcus either from the sputum or blood stream in eighty-three of the cases, in the remaining seventeen cases we were not able to detect the specific pneumococcic organism from the sputum or blood stream although in several instances we were able to find the group to which they belonged. As noted on the table, we have not included three fatal cases which received treatment for less than twelve hours. These represented terminal

\* Presented January 17, 1939 before the Section of Medicine

TABLE I

Type	Number	Deaths	Type	Number	Deaths
I	21	0	XIV	5	0
II	7	0	XV	2	0
III	14	3	XVI	1	0
IV	5	1	XIX	2	0
V	5	0	XXIII	1	0
VI	4	0	XXVII	3	0
VII	6	0	XXX	1	0
VIII	6	0	Others	17	1
	<u>68</u>	<u>4</u>		<u>32</u>	<u>1</u>

## TOTAL

Cases 100 Deaths 5

(3 fatal cases treated for less than 12 hours not included)

TABLE II

Toxic Reactions	Number
Nausea	42
Vomiting	
Troublesome	24
Severe	9
Dermatitis	1
Acute Hemolytic Anemia	1
Leukopenia	1
Drug Fever	1

cases of pneumonia which received no more than two doses of the drug and for that reason I did not think that we should include them in the above report

Naturally, when a new drug is being considered, the first question that comes into the mind of the physician is, what are the toxic effects of this preparation? As far as the toxic reactions, as can be seen by Table II, the gastrointestinal symptoms are the most important. In any acute infection, as pneumonia, we expect a certain amount of gastrointestinal irritability, and it is not surprising that the oral administration of the drug should result in some untoward reactions. The problem of vomiting is the most important toxic reaction which confronts us at this time. As we all know there is a definite chloride deficiency during pneumonia, and with this added vomiting we get a marked loss of chlorides. With this in view we have given rather large dosages of salt solution intravenously, and believe that this procedure has diminished the severe vomiting. In

a number of instances the discontinuance of the drug for one or two doses has brought cessation of the vomiting. We have also introduced the drug through a nasal catheter into the duodenum with beneficial results. Rectal administration has proved unsuccessful. As noted on Table II, we have made no reference to cyanosis as a toxic reaction. We have seen rather severe cyanosis in about 10 per cent of our cases, but it is difficult to determine whether the cyanosis is due to the drug or is associated with the pneumonia. In closing, I wish to say again that we are quite enthusiastic thus far regarding the efficacy of sulfapyridine in the treatment of pneumococcal infections.

# PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA\*

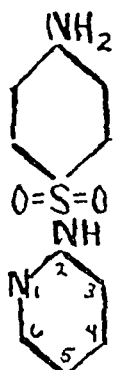
*The Absorption, Acetylation and Excretion of Sulfapyridine*

H E STOKINGER

I WILL attempt to review briefly some preliminary analytical results on the fate of sulfapyridine (M & B 693) in laboratory animals and patients at the Presbyterian Hospital, Columbia Medical Center

It should be said at the outset that M & B 693 bears certain analogies to sulfanilamide 1) the detoxification process is one of acetylation, 2) it may be estimated quantitatively in body fluids by methods that involve no new procedure This latter allows the drug to

*Free form Sulfapyridine*



*Conjugated form Acetyl-sulfapyridine*

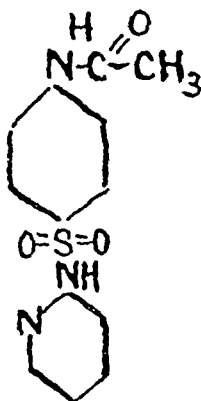


Fig 1—Detoxification of M & B 693 in Man and Rabbits

be followed in a fairly convenient manner during its course through the body

The formula on the left represents the chemical constitution of the M & B 693, officially named recently Sulfapyridine by the American

\* Presented before the Section of Medicine, January 17, 1939

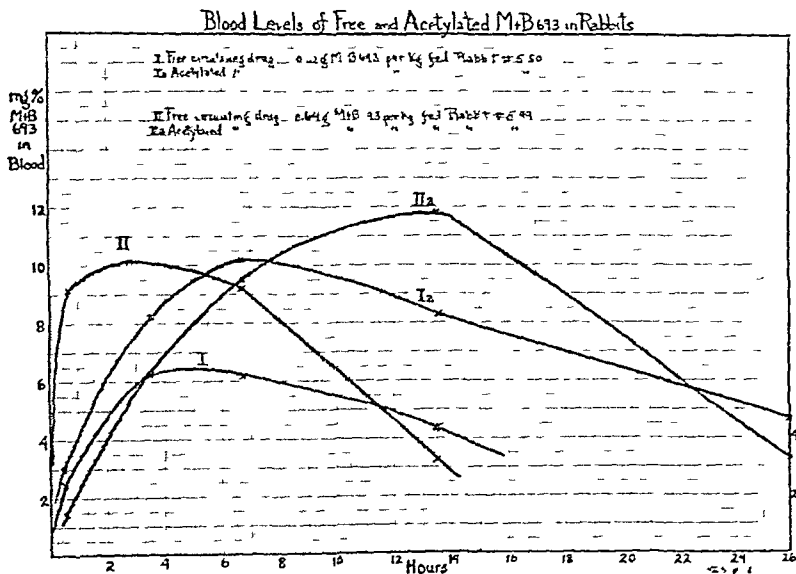


FIG. 2 Blood Levels of Free and Acetylated M+B 693 in Rabbits  
 I Free circulating drug 0.32 g M+B 693 per Kg fed Rabbit No 550  
 Ia Acetylated ' drug 0.32 g M+B 693 per Kg fed Rabbit No 550  
 II Free circulating drug 0.64 g M+B 693 per Kg fed Rabbit No 599  
 IIa Acetylated ' drug 0.64 g M+B 693 per Kg fed Rabbit No 599

Medical Association As the drug circulates in the body it is conjugated with acetic acid, presumably by the liver, to form the compound having the constitution represented on the right This compound is more insoluble than the free form and may be isolated in pure crystalline form in the urine of patients receiving the drug

The amino ( $\text{NH}_2$ ) group is also utilized in quantitative estimation of M & B 693 The method depends upon diazotization at  $0^\circ\text{C}$  with nitrous acid and coupling with a suitable organic moiety to give a dye that may be compared colorimetrically against known standards The conjugated form is determined after hydrolysis of a protein-free filtrate This reduces the drug to the form on the left and colorimetric analysis is as above outlined Since this procedure gives total circulating drug (free plus conjugated) the amount of drug conjugated is obtained by difference of analyses for the total and free drug

Such analyses have been made on a number of rabbits receiving a single dose of the drug by stomach tube Figure 2 shows the rate of



absorption, acetylation and excretion in two typical instances. Curve I gives the blood level of the free drug at varying intervals. It shows that the drug is immediately absorbed into the blood stream upon ingestion, appreciable blood levels being obtained within thirty minutes. In three to four hours a maximum is reached which is maintained for some three to four hours. Blood analyses twenty-four hours after ingestion show no free circulating drug. Curve Ia is the corresponding curve of the acetylated form. A definite lag is noted both in its initial and final phases. After twenty-six hours appreciable quantities of the acetylated form are still present in the blood.

Curves II and IIa for a rabbit on double the dose of curve I show similar results.

Table I shows the same type of analyses in tabular form made on patients receiving the drug over a usual course of therapy. Superscripts in cases 1, 2, and 3 indicate results of blood levels during initial phase of drug administration. Considerable variation in the acetylated values is noted. The second row of figures shows representative results of blood levels on the dosages given after a steady state had been obtained (usually forty-eight hours after initial dose). Case 4 is representative of the final phase and shows no free circulating drug twenty-four hours after the last dose.

The actual blood levels attained from a given dose are felt to depend on three factors: (1) the rate of absorption, (2) rate of acetylation and, (3) the rate of excretion. Evidence for the modifying effect of the rate of absorption is given in the first case, Table II. These were analyses on a patient with gastrointestinal obstruction which gradually cleared with consequent rise in blood levels. It is noteworthy that the per cent of acetylation remained approximately constant.

The ability of individuals to acetylate sulfapyridine varies between twenty-five and ninety per cent. Cases 2 and 3 of Table II are representative blood levels for patients with slight tendency to conjugate the drug.

The effect on blood levels of patients conjugating the drug to a high degree is given in the two comparative cases of Table III. Though both patients were on the same dosages, blood analyses made every three or four days reveal entirely different pictures. The free circulating drug in the second case is approximately three times that of the first. A possible explanation is to be found in the values of per cent acetylation which in the first case might be thought of as depressing the amount of free circu-

TABLE I  
M+B 693 HUMAN BLOOD LEVELS

	DOSAGE <i>gm /diem</i>	FREE <i>mgm per cent</i>	TOTAL <i>mgm per cent</i>	ACETYLATED <i>per cent</i>
Case 1	{ 5.5, 6, 6 6	5.5 10.5	5.5 14.2	0 <sup>1</sup> 30
Case 2	{ 2, 2.5 2	2.5 1.2	4.1 3.3	39 64
Case 3	{ 3, 3 3	2.0 3.7	2.4 6.5	15 43
Case 4	3, 3, 3	0.0	4.0	100 <sup>4</sup>

Sample for analysis after

- 1) 20 hrs 1 gm q4h  
2) 10 hrs 1 gm q4h  
3) 6 hrs 1 gm q4h  
4) 24 hrs after last dose

TABLE II  
M+B 693 HUMAN BLOOD LEVELS

	DOSAGE <i>gm per diem</i>	FREE <i>mgm per cent</i>	TOTAL <i>mgm per cent</i>	ACETYLATED <i>per cent</i>
Case 1	{ 4, 3.5, 3 3, 1.5	2.0 3.5 5.5	3.5 8.0 10.5	43 56 48
Case 2	{ 4, 3.5 1.5	3.0 10.5	4.5 13.0	33 19
Case 3	5, 5, 2	7.5	10.0	25

TABLE III  
M+B 693 HUMAN BLOOD LEVELS

	DOSAGE <i>gm per diem</i>	FREE <i>mgm per cent</i>	TOTAL <i>mgm per cent</i>	ACETYLATED <i>per cent</i>
Case 1	3 gm daily for 22 days	1.2 1.5 3.0 2.5 1.5 1.0	3.0 8.5 10.0 6.2 6.5 5.3	60 83 70 60 77 81
Case 2	3 gm daily for 5 days	6.9	14.1	51

TABLE IV  
M+B 693 IN URINE OF PATIENT  
EXCRETION OF M+B 693

DOSAGE M-B 693 <i>gm per diem</i>	FREE <i>mgm per cc</i>	TOTAL <i>mgm per cc</i>	ACETYLATED <i>per cent</i>	DAILY TOTAL <i>gm</i>
4				
6	0.437	1.56	72.0	2.18
5	0.686	2.80	76.0	2.70
6	1.006	4.12	75.5	(2)* —2.66
1	0.600	4.00	85.0	(15)* —2.0
	0.00	0.16	100.0	0.12
	0.00	0.04	100.0	0.04

\* Crystals of acetyl compound recalculated as free

TABLE V

RELATION BETWEEN ACETYLATION AND  
EXCRETION OF M+B 693

	<i>Total Drug given in gms</i>	<i>Acetylation per cent</i>	<i>Recovery in Urine per cent</i>
Case 1	16.5 in 5 days	30-40	82.5
" 2	22 in 5 days	30	72.5
" 3	22 in 5 days	55-65	57.5*
" 4	22 in 5 days	75-80	48.0
" 5	30 in 10 days	80-90	49.0
" 6	15 in 5 days	Variable due to renal shut-down	16.0

\* Value low, as urinalysis was stopped upon withdrawal of drug

lating drug by conjugation. Urine analyses on this patient gave acetylation values of eighty-five to ninety per cent. Three months later the patient on the same dosage gave the same blood and urine analyses.

Table IV gives urine analyses for both free and conjugated forms. Constant values of acetylation again appear where presumably the rate of absorption is sufficiently high (first three lines of table).

In testing the efficacy of any new drug, it is important to know the amount excreted. Total urinary excretion varies considerably among patients as shown in Table V in which an inverse relation between amount of acetylation and excretion is found to exist in many cases. The per cent recovery of drug in Case 3 is low, as the urine samples were stopped on withdrawal of the drug. Other cases, not given here, on larger doses with the same per cent acetylation, appeared to eliminate relatively less in the urine. When renal activity is disturbed as in Case 6 very small amounts of the drug are recovered in the urine.

## CONCLUSIONS

Blood analyses on seventy-five patients for sulfapyridine show

- (1) Sulfapyridine appears in the blood stream directly after ingestion
- (2) During circulation, the drug is detoxified by acetylation
  - (a) The amount of acetylation varies between twenty-five and ninety per cent
  - (b) This amount appears to be constant and characteristic for an individual

- 
- (c) With abnormally low blood values of free drug are frequently found high acetylation values
- (3) The amount of circulating drug depends on three factors Rate of absorption, acetylation and excretion Acetylation appears to vary most among individuals giving rise to major differences in blood levels on given doses
- (4) Essentially all of the free sulfapyridine is eliminated in twenty-four hours, the acetyl form in forty-eight hours
- (5) Urine analyses confirm these findings In addition fifteen to eighty-five per cent of the drug administered has been recovered in the urine The variation appears at present to depend on (a) dosage, giving an inverse effect the larger the dose the less proportionally is found in the urine (b) Renal activity direct effect The less the urine volume, the less the drug (c) Acetylation inverse effect the less the acetylation the more the drug recovered in urine
- (6) Blood levels on adults receiving 3 gms daily normally show 4 to 6 mgm per cent, those receiving 6 gms daily normally show 10 to 13 mgm per cent

## THE TREATMENT OF DEPERSONALIZATION\*

PAUL SCHILDER

DEPERSONALIZATION is a state of the personality in which the individual feels changed in comparison to his former state. This change extends to both the awareness of the self and of the outer world and the individual does not acknowledge himself as a personality. His actions seem automatic to him, he observes his own actions like a spectator. The outer world seems strange to him and has lost its character of reality. We find, therefore, in this picture changes of the self or depersonalization in the narrower sense, and changes in the environment, or feelings of unreality, alienation of the outward world, "Entfremdung der Wahrnehmungswelt." For this latter phenomena, Mapother, Mayer-Gross,<sup>1</sup> Guttmann and Maclay<sup>2</sup> have suggested the term, derealization. Pictures of this type occur according to my own studies,<sup>3</sup> Haug<sup>4</sup> and Mayer-Gross<sup>1</sup> in a great variety of clinical conditions. The picture has been observed as a passing phenomenon combined with *déjà vu* in the normal. It may appear in connection with organic diseases of the brain, especially before and after epileptic attacks. It has been observed in depressive psychoses and schizophrenia. In the beginning and in the phase of disappearance of severe neuroses it is not uncommon.

However, this picture occurs also as the dominant symptomatology of a very severe and chronic type of a specific neurosis. Patients of this type complain year after year about their changed experience concerning the self and the world. Cases are on record with a duration of twenty or thirty years. This study deals merely with this nuclear group, the neurosis depersonalization.

The philosophical and psychological interest which these cases offer is considerable. Taine<sup>5</sup> was the first to use the picture as proof for his philosophical theories of perception. Besides the complaints of changes in perception and emotions there are complaints concerning the experi-

\* Read at the meeting of the Section of Neurology and Psychiatry of The New York Academy of Medicine and the New York Neurological Society, January 10, 1939. From the Psychiatric Division of Bellevue Hospital, New York, and from the Department of Psychiatry, New York University Medical College.

ence of one's own body and about changes in the perception of time and space. Accordingly, the philosophers have used every one of these complaints as proof that this particular function is the most important one in our relation to self, body and world.

The picture of depersonalization has also attracted the attention of psychoanalysts, among whom I may mention Sadger,<sup>6</sup> Nunberg,<sup>7</sup> Reik,<sup>8</sup> Federn,<sup>9</sup> Oberndorf,<sup>10</sup> Bergler and Edelberg.<sup>11</sup>

The various authors have stressed different sides of the psychological problems. Reik stresses the constant self observation which according to his opinion is based on sadomasochistic attitudes. Oberndorf puts the main emphasis on the erotization of thought and especially upon the wish to adopt the way of thinking of the opposite sex. Other authors stress the exhibitionistic and voyeuristic components in the picture. Bergler and Edelberg are of the opinion that there is a strong tendency to anal exhibition. This exhibition is transformed into an increased tendency to self observation. I am inclined to stress the fact that the patient with depersonalization has been admired very much by the parents for his intellectual and physical gifts. A great amount of admiration and erotic interest had been spent upon the child. He expects that this erotic inflow should be continuous. The final outcome of such an attitude by the parents will not be different from the outcome of an attitude of neglect. Dissatisfaction has to ensue even if the parents live in a state of continual admiration of the child since every such relation does not consider the child as a total human being but merely as a show piece. The dissatisfaction and deprivation of the child has to express itself in an increase of aggressive and submissive tendencies. These combine with sexual tendencies to sadomasochism. Finally, by identification with the parents self observation will take the place of the observation by others. The self observation will be blended with sadomasochistic tendencies. The individual will at first be able to admire his body as well as his thinking. Since such a detachment from the love object cannot remain satisfactory the self adulation will be followed by hypochondriac signs. To the denial of vision in the sphere of perception is now added the loss of admiration of one's self. The individual, however, does not completely give up and will at least enjoy the self observation which represents the sadistic components as well as the voyeuristic and narcissistic (self-admiring) ones. The patients, furthermore, preserve their intellectuality in this way and are able to continue their activities in the social and physical world which

may appear outwardly successful although empty of emotional satisfaction for the individual. Depersonalization is the neurosis of the good looking and intelligent who want too much admiration.

It is understandable that a neurosis of such depth will need a psychotherapy of long duration. The best observers in this field agree on this point. Oberndorf, for instance, has treated his cases for a long time and Bergler and Eidelberg write as follows: "We think that this absolute pessimism (concerning the treatment) is not justified, however, it is a prerequisite for the therapy that one knows the mechanisms and starts on the right point. Furthermore, very long time is necessary. While the analysis of a more severe case of obsession neurosis takes at least two to two and one-half years, the double space of time is the requirement for the treatment of depersonalization. It does not seem to be very hopeful if one demands half a decennium for a treatment. However, '*amicus Plato, magis amica veritas*'" The experiences of Oberndorf and myself are, however, better. Some of my cases were treated with individual psychoanalysis, some of them were treated in group psychotherapy. Two cases may be mentioned shortly.

Rose H. came for treatment at the age of twenty-five with depersonalization symptoms which had existed for two years. She was good looking and of superior intelligence. As so often occurs, the symptoms had suddenly started during an episode of petting in which she had felt that she had lost herself and her emotions. Her sexual feelings also vanished suddenly. This episode had followed an incomplete and disappointing love affair with her employer. The final rejection by him had revived the humiliations she had experienced in early childhood from her father. The psychological treatment led to a recovery after two years. The symptoms disappeared completely, however, one year after the treatment, the patient had not yet made a sexual adaptation.

Gertrude W. came for treatment at the age of twenty-one. Depersonalization symptoms had persisted for several years. She complained "that things were moving up and down before her eyes." "I feel my head is empty. There is only a blank inside. It is as if I would be asleep all the time. I do not realize how time passes. My whole intelligence and personality have disappeared. I have no desires anymore. I might as well be dead. My voice has changed completely. Sensations are present but they do not reach my head." The patient had also a wealth of hypochondriac sensations which pertained particularly to her abdomen. She

was very much concerned about her anal functions. A great hostility concerning the mother reached back into early childhood. There were very lively sadomasochistic phantasies since the age of five. The patient was treated with group psychotherapy and lost almost all her symptoms, however, in this case, also no sexual adaptation was reached.

Three other depersonalization cases were treated by L. Bender with good results. However, several years later all three cases relapsed under difficult outward situations. In one of my cases no therapeutic result was achieved in three months and the patient discontinued the treatment. In two cases psychotherapy resulted in minor gains. These cases will be mentioned later in another connection.

We may summarize by saying that psychotherapy in depersonalization cases takes a great amount of time, is technically difficult, does not always remove all problems and does not protect the patient from relapses. However, there is no question that every case of depersonalization needs a great amount of psychological help, and there is no reason to be pessimistic concerning psychotherapy in these cases. The treatment has to be psychoanalytic or has to utilize psychoanalytic insight.

Considering the difficulties of the psychotherapeutic approach one might ask what could be done for these patients by medication. I have occasionally tried benzedrine in depersonalization cases, however, the results were passing and the psychotherapeutic approach was in no way helped by the medication. Guttman and Maclay<sup>2</sup> have studied the influence of mescaline on depersonalization symptoms insofar as they consist of changes of the surroundings (derealization) but not of the self. However, this improvement was of short duration, not lasting longer than one day. The authors come to the conclusion that it may be used as an adjuvant for psychotherapeutic activity. A drug which brings a relief of short duration is obviously not of a great therapeutic value with such chronic problems. It is usually not very helpful in psychotherapy when one proves to the patient by the temporary relief with drugs, that he can feel better. Drugs which allow the patient to come to a deeper insight by increasing the transference situation and changing the state of consciousness help the psychotherapeutic approach much more than drugs which merely relieve symptoms. Sodium amytal may act in such a way. It has not been tried in depersonalization cases. I have myself tried to use benzedrine<sup>12</sup> as a help in revealing psychotherapy of neuroses. However, as mentioned above such results were not achieved in depersonalization cases.



The modern methods of treatment for schizophrenia have only been tried occasionally in severe neuroses. Glueck<sup>13</sup> mentions in one of his publications a case of severe obsession neurosis which improved by insulin treatment. In the series of cases treated in Bellevue, one case of severe obsession neurosis reacted only temporarily to the treatment. At Bellevue we generally found the application of metrazol therapy simpler from a technical point of view<sup>14</sup> and decided therefore to make an attempt to treat this particular type of neurosis with metrazol. The depersonalization cases constitute a comparatively well defined group of neuroses. The psychotherapeutic approach to these cases is difficult. Results obtained in such a group with metrazol might be of use in evaluating the treatment for neurosis in general. We have followed the technique of Meduna<sup>15</sup> and use a 10 per cent aqueous metrazol solution. Injections were given intravenously in doses varying from 4½ to 15 grains. We tried to produce three convulsions in a week. One case may be reported in a short abstract, as an example.

Johanna L., thirty-one years old, comes from a family in which the father and one aunt had severe psychotic states probably of manic-depressive character. She was always considered an outgoing personality. Also her brothers and sisters were energetic and successful. She was the oldest of five children, three girls and two boys. She had two children, one of whom was only a few months old when the patient got sick. The family was at that time in straitened financial circumstances. The illness started five months before admission to Bellevue Hospital. She complained that she always felt too tired and was disinclined to sexual intercourse. She ate very little and claimed that she had lost her sense of taste. She thought this was as a result of a cold. She became untidy in appearance and was preoccupied with the care of her children. She complained that she had lost interest in things, that she didn't belong to this world and that she couldn't cry. She was sent to a sanitarium. There she stated that she was not alive but had turned to stone and had no feelings and no emotions. In the sanitarium she swallowed several needles with suicidal intent, and was, therefore, sent to Bellevue Hospital, on September 10. She said "I can't live, I don't feel at all, I just got fear of life, everything became complicated, everything turned in me, the whole world just looks flat. Nobody can help me. It feels as if I had no place on earth, nothing in the world belongs to me, I don't feel that my family and children belong to me, life has been taken out of me, I seem to be inside out

Everything looks backward, the heart doesn't seem to be in the same place, I can't change, just like a chair over there. It is as if the eyes would look inside instead of out. Time neither passes nor stands still. It doesn't seem like another day, there is no penetration of enjoyment. My mind goes round and round all the time in circles, the whole world looks flat to me. I know what torture you and everyone else is going through but no torture is greater than my misery." On the ward she was seclusive and did not talk spontaneously. However, she was very productive when one talked with her. On one occasion, she tried to grab iodine in order to drink it.

On October 4th, metrazol treatment was instituted. She received  $4\frac{1}{2}$  grains intravenously and had no convulsion. From then on, up to the seventh of November, fifteen convulsions were produced, the first four with injections of 6 grains, the subsequent three with  $7\frac{1}{2}$  grains and the last eight with 9 grains. There were no particular incidents during the treatment. The improvement started after the third convulsion and progressed steadily. The clinical symptoms had practically disappeared after the tenth injection. The patient was discharged fully recovered and with full insight, but she still receives psychotherapeutic help.

We have treated nine cases so far. Table I shows the most important features of these cases. The patients were treated in the hospital with the exception of two who were treated in the out-patient department. These two patients, however, could not be induced to have more than three convulsions. They felt improved but experienced a sensation before the convulsion so terrifying that they did not want to continue voluntarily. We have had the same experience in other patients whom we tried to treat in the out-patient department. We have discussed all the details of the treatment, not only with the patients, but also with the relatives and treated only those patients who could themselves be convinced that the treatment might be effective. There were no untoward incidents in the treatment, except that one patient dislocated his shoulder, but the effects of this had disappeared in a few days.

Not much has to be added to this table. Everyone who has worked with depersonalization cases will agree that the results surpass the results reached by other methods. One may doubt the diagnosis in the one or the other case, for instance, in the case in which emotional flatness is noted. This case was diagnosed by others as one of schizophrenia. The borderline between endogenous depression and depersonalization may be

## TABLE I

## NINE CASES OF DEPERSONALIZATION TREATED WITH METRAZOL

Name	Age	Additional Symptoms	Duration Before Treatment	Previous Psychotherapy	Number of Conulsions	Maximal Dose in Grs	Result
J L	31	Suicidal attempts Severely depressed	5 months	Incomplete	15	9	Cured
R O	29	Slight residual signs of previous encephalitis	Several weeks	None	9	9	Cured
L R	31	Severe psychological conflicts for years	4 months	Incomplete	10	15	Much improved
S H	30	Neurotic conflicts preceding suicidal attempts	1 year	Incomplete	7	7½	Improved
B A	19	Catatonic pupils	3 months	None	8	13½	Cured
S S	32		4 years	Moderate improvement	3	10½	Further but still incomplete improvement
S R	18	Hears his own voice continually as obsession	15 months	None	25	12	Improved
W I	23	Flatness of emotions	4 years	Incomplete	22	10½	Slightly improved
A S	26		4 years	Partly successful	3	10½	Further but still incomplete improvement

sometimes difficult to draw. However, these diagnostic difficulties lie in the nature of the subject.

It is obvious that insulin and metrazol treatment have a field of application also outside of the field of schizophrenia. They have been variously tried in manic-depressive psychoses. My own experience with the metrazol treatment of manic depressives is too small, however, there were startling results in two cases of confused mania (the only ones treated). I have also observed improvements in depressions. Bennett<sup>16</sup> reports that ten consecutive severe depressive psychotic patients have all been relieved by shock therapy. He reports that the improvement started two weeks

after the treatment began. He also quotes literature which asserts that hysteria and anxiety cases derived benefit from metrazol treatment insofar as the patients established a better rapport for psychotherapy after its use.

In most of our cases the first signs of improvement appeared after the first three or four injections, and in the majority of cases the symptoms disappeared after about six to ten injections. We find it advisable, however, to give two or three more injections after the symptoms have cleared up. The symptoms may disappear without further psychotherapy, even then, the individuals always have unsolved psychological problems. I am, therefore, of the opinion that every depersonalization case which is treated with metrazol needs extensive psychotherapy even after he is free from manifest symptoms. We have acted accordingly in all cases in which the outward circumstances made the application of psychotherapy possible. This is the same point of view which Orenstein and myself<sup>17</sup> have taken in respect to insulin and metrazol treatment of schizophrenia.

One may, of course, raise the question whether the results of this treatment of depersonalization are merely due to psychological factors connected with the treatment. The patient experiences indeed terror and fright and even a threat of death. The transference is increased when he regains consciousness. However, it seems to me that such psychological phenomena are obviously the reflection of deep-lying changes in the organic functions. Furthermore, experience shows that deep-lying neurotic pictures cannot be influenced by mere fright. I am, therefore, of the opinion that organic changes in the brain function connected with metrazol treatment have a therapeutic effect on the depersonalization neurosis. It is not possible to say at the present time whether one can generalize this statement for other neurotic conditions. It is even too early to state that the cure in depersonalization cases and in manic-depressive psychosis and schizophrenia will be a lasting one. However, one of my recovered depersonalization cases is free from symptoms and has worked steadily for more than ten months.

#### SUMMARY AND CONCLUSIONS

1. The picture of depersonalization is a rather well circumscribed chronic neurotic picture which offers great difficulties for psychotherapy. However, by psychoanalysis or methods akin to psychoanalysis good

results can be obtained if the treatment is continued for years

2 Treatment with mescaline and benzedrine is ineffective

3 Nine cases are reported in which the intravenous treatment with metrazol in doses sufficient to give convulsions, gave good results. However, some of the cases were not completely cured

4 This treatment should be combined with psychotherapy

5 The effects of treatment are probably due to organic changes. The psychological effects of the drug treatment are not sufficient to explain the results

6 Metrazol treatment is not only effective in schizophrenia but also in manic-depressive psychoses and in specific types of chronic neuroses. The question arises whether other types of so-called psychogenic disturbance (neurosis) will be responsive to this treatment

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*Discussion*

MANFRED SAKEL

The paper of Dr. Schilder is one of great interest. It is indeed an important step in the endeavor to treat neuroses somatically. I do not dare to discuss the psychological aspects of depersonalization since Dr. Schilder is one of the most experienced in this matter. No doubt those who expect me to defend the wholly somatic point of view will be disappointed. It is therefore fortunate that there is no need now for such a dualistic defense.

Depersonalization should be considered as a kind of dysfunction in the perception of the own personality. This definition by itself brings up a very difficult question. To discuss the related problems would force me to define the meaning of the term "personality," itself. I do not wish to involve myself in these far-reaching spheres. I may only call your attention to the fact that there are symptoms in many other diseases which could easily suit this group. These are diseases which, it is generally assumed, do not derive from psychologic sources only. I would like to emphasize the fact that similar experiences occur in the onset of schizophrenia, as Dr. Schilder mentioned. The schizophrenic often feels himself estranged from the external world, and the surrounding environment has a changed significance to him. He perceives new, peculiar and quaint features which he did not notice before, from without as well as from within.

It seems to me that the normal picture of the world and the feeling of being familiar with it, as well as a feeling of being familiar with one's own psychological condition, should be always considered as bound to normal functions of the brain. It seems to me too that every change in the organism and especially in the functions of the brain is perceived in some way by the individual self. One may imagine it as a kind of a switch-board on which the red-lights can be flashed only when disturbances occur which bring them to our perception, but normally there is no realization at all because no red-light flashes occur.

These warning signs may come from two different sources. From the pathways of perception (when confusion or "short-circuiting" result in hallucinations), and secondly from disturbances of self-perception. These experiences are both an expression of the dysfunction of the brain.

This statement does not exclude the fact that this dysfunction can be and frequently is induced by psychological causes. One recalls the known example of the cat which shows stormy intestinal movements while stroked in the wrong direction. Everyone will admit that these movements are, in the final analysis, induced by biochemical stimulation. Doubtless everyone will admit also that the releasing cause was the feeling of discomfort. The culmination of this result can be achieved from both poles.

I may stress that some cases of neuroses have a special tendency for biochemical dysfunction. A slight psychological cause is sufficient to release the symptoms. Dr. Schilder at the end of his paper pointed out that somatic changes are finally and basically responsible for neurotic symptoms. Although there are further additional questions which unfortunately cannot be thoroughly discussed in brief, this is the point in which I generally agree with him. May I add that at the beginning of the pharmacological shock treatment of psychoses, I treated a great number of patients including almost all diseases within the psychiatric range. It happened that I was able to treat among them quite a number of those with symptoms of depersonalization. It is true that the results were most satisfactory, however, I did not publish the results, being afraid that I would be charged with claiming to possess a cure for all maladies.

It is regrettable that Dr. Schilder did not have the opportunity to watch the development of this shock treatment from the beginning. I recognized very early, that the production of convulsions, *per se*, is not efficient enough a factor, in the combined therapeutic procedure to be used alone effectively. Although administration of metrazol without insulin is certainly easy, no advantage could be seen either for the doctor or for the patient. For this reason I treated also the patients with obsessional neuroses and patients with symptoms, as described principally by Schilder in the usual way. I used the metrazol to provoke the imminent convulsion in hypoglycemia about two to three hours after the application of insulin. The terrifying effect of the preconvulsion period was entirely eliminated. In our cases no fears were observed, therefore no objections were made, and no necessities occurred to stop the treatment. But this is relatively of less importance. Mainly I would like to point out my belief that the effect in quality and also in the duration was much better by applying the treatment as I described it.

In these cases the metrazol doses to provoke a convulsion during the

hypoglycemia average about one-third of the doses which Dr. Schilder mentioned, this factor is not to be neglected. In some patients, who did not show depersonalization symptoms at all during their illness, these symptoms were manifested in a marked degree for a short time after the patients' awakening from coma. An obsessional neurotic, for example, reacted in this manner and one patient with schizophrenia whom I described in my book. I did not keep records of the duration of improvement in cases of neuroses and so cannot say much about this, but in two patients whom I treated in the above-described manner, I was informed of progress for a period of two years. One was an executive who had to neglect his business for a few years due to his illness. After the treatment he was able to assume again the responsibility of his business and, as I was told, very successfully. He was still doing so when I last heard of him.

### *Discussion*

LOUIS WUNDER

Since Dr. Schilder's paper deals with the treatment of depersonalization, I shall not enter into the psychodynamics of this disorder and its treatment by psychotherapeutic means alone. There is no doubt that there are underlying psychological factors in this symptom complex. Depersonalization, *per se*, is not a disease entity, but a symptom prevalent in many mental disorders. It is common in schizophrenia and manic-depressive psychoses, and also in chronic psychoneuroses. Although each individual may describe his symptoms somewhat differently, the concurrent syndrome is that the outer world seems strange, there is a feeling of unreality and an estrangement from the outside world. There is a loss of "feeling tone." This symptom is so common among hospital patients with functional disorders that one is at a loss, at times, to overcome it even with intensive psychotherapy. Dr. Schilder tonight has demonstrated to the Society the fact that depersonalization, whether as a symptom alone or associated with other symptoms of mental disease, can be overcome by the use of chemotherapy.

At Hastings our experience with meprobol has given us the same results as those reported by Dr. Schilder. We have administered meprobol to forty-three patients, completing the course with thirty-six. Twenty-



one of these were suffering from chronic psychoneuroses and depressions in which the depersonalization syndrome was very marked. Of the fifteen others manifesting a schizophrenic reaction, only a few presented any depersonalization symptoms. Our results were very satisfactory. As a matter of fact, we are of the opinion that in depressions where the stupor is not very deep, where there is no retardation, but where there are marked symptoms of depersonalization and feeling of unreality, metrazol has a very beneficial effect in accelerating the rate of recovery. The common statement that depressions get well anyway, even without chemotherapy, is probably true, but metrazol precipitates an earlier recovery and perhaps breaks up the manic-depressive cycle. I make this statement on the basis of our experience with two patients, both manic-depressives, one with obsessional thinking, one with a depersonalization syndrome. The latter had two previous attacks each lasting about a year, the other was also sick previously for about nine months. In each case the depression was followed by a hypomanic phase. Both recently had a recurrence of their episodes and were hospitalized, and we decided to give metrazol to both. To our great surprise both cleared up rapidly, the duration of hospitalization in one case being seven weeks and in the other, about ten. One left the hospital in July and the other in September, neither showed subsequent hypomanic reactions and both are doing well at present. This, of course, requires further study and verification.

I am in agreement with Dr. Schilder that metrazol and insulin are not the only remedies in the treatment of the chronic psychoneuroses, that these persons require psychotherapy and that the psychotherapy should be started as soon as the patient begins to show response to the chemotherapy, that furthermore, the administration of metrazol should not be discontinued suddenly but should be reduced gradually. In our experience at Hastings, after the patient begins to show definite improvement, the treatment is reduced at first from three times a week to twice a week and later to once a week, the patient in the meantime receiving intensive psychotherapy. After the injections are completely discontinued, active psychotherapy is continued until the patient is discharged. We believe that this prevents a recurrence of the mental disorder. Thus far, none of the metrazol cases in our group that recovered or showed improvement have returned to the hospital.

How metrazol works I am unable to state. Personally I do not think it is a fear phenomenon, for our experience has shown that if the patient

does not get a good convulsion, he does not show the proper response, and the patient's fear when there is no convulsion is much greater than when the patient gets a seizure. As a matter of fact, the fear of impending death is so marked if there is no convulsion that the patient sometimes refuses to take another injection unless he is promised that the dose will be large enough to give him a convulsive seizure. Repeated injections without convulsions do not produce any change. On the other hand, if there is going to be a response, one notes an improvement after the third or fourth consecutive convulsion. Therefore, if we are going to assume that the reaction is due to fear, this fear probably touches the deep unconscious, but certainly it is not conscious fear that gets them well. The probabilities are that the metrazol seizures disturb the biochemical relationship in the system, perhaps discharging certain toxins and reorganizing the cortical functioning.

Our experience has also shown that metrazol can be used in severe chronic psychoneuroses, especially of the obsessional type, or the chronic anxieties. At present we have a patient, a severe compulsion neurotic of three years' duration, who prior to coming to Hastings received psychoanalytic treatment for ten months and was just able to get along. When admitted to the hospital, he was so full of obsessions and compulsions that it would take him hours to dress and undress. It would take him a whole half hour to wash his hands. He was afraid to touch anything and even to say anything because he was afraid that his words might hurt someone. He was so obsessed that he even felt his very presence might hurt people and, as a result, he would stay in his room for hours at a time before he would decide to go out. When the family wanted him to go out of the house, they resorted on several occasions to putting some strong disinfectant in his room in order to choke him out. This patient received eighteen metrazol injections and by the time he had had the twelfth, we were amazed to note the change in his condition. Practically all the obsessions enumerated above have disappeared. He even works around the hospital, cleaning, uses his hands freely and enters readily into conversation. This patient is at present under active psychotherapy in order to try to remove some of the deeper underlying mechanisms in the hope that we may change his character thinking.

Dr Schilder should be congratulated on bringing this interesting topic and this form of treatment before the Society for there are a great many patients whose financial status does not allow them the luxury of

undertaking an analysis of a year or two in the hope of getting their difficulties adjusted, and there are also many people whose intellectual constitution is such that, even if they can afford the money, analysis is of no avail. We who practice among the former group have to resort to various means of getting them back to society, and if metrazol can remove the symptoms and make the individual a useful member of his social group it should be tried on all patients who fail to respond to psychotherapy or in whom the duration of illness is over a year.

## PRESENT STATUS OF PROTAMINE INSULIN\*

HERMAN LANDE

THE effective retardation of the action of insulin by combination with protamine promised a new era in the treatment of diabetes. The demonstration that the addition of zinc to this compound not only increased its stability but enhanced its hypoglycemic value resulted in the preparation now in general use. Protamine zinc insulin has been available commercially for two years. The early enthusiastic reports have been somewhat tempered by further experience but in the light of that experience we are better able to evaluate its advantages and disadvantages. The prolonged action of protamine insulin has been amply confirmed and careful studies in fasting patients have indicated that it may be effective for as long as forty-eight to seventy-two hours. Obviously a more stable blood sugar level can be maintained than with a soluble insulin whose activity is limited to approximately six hours. There is, however, an important distinction between the availability of protamine zinc insulin throughout the twenty-four hours and the physiological action of the normal pancreas. Unfortunately, insulin is liberated from the subcutaneous depot of protamine zinc insulin at a constant rate independent of the physiological requirements of the body, even after the ingestion of carbohydrate.

Reports from large groups throughout the country disclose a marked variance in the results obtained with protamine therapy, ranging from 30 to 80 per cent of satisfactorily controlled cases. However, it should be borne in mind that statistical studies of diabetes are especially misleading. Diabetics differ in their response to treatment and clinics differ in their criteria of satisfactory control. In fact, one of the most disconcerting results of the introduction of protamine zinc insulin has been the lowering of the standards of diabetic control.

The varying response of diabetics to treatment is of especial importance in evaluating the results with protamine zinc insulin. The obese

\* Delivered December 21, 1938 at the joint meeting of the Section of Medicine and the New York Diabetic Association.

adult type is as a rule easily controlled by dietary restrictions with or without the use of insulin. A moderate dose of protamine zinc insulin given once a day is often sufficient to maintain a persistently sugar-free urine and a fairly stable blood sugar level in adults who have been previously controlled by thirty units or less of regular insulin. Protamine zinc insulin is an almost ideal therapeutic agent for this group of patients so far as convenience and control of glycosuria are concerned. Fortunately, the great majority of diabetics are of this type.

The juvenile, adolescent and early adult diabetic have frequently presented difficulty in treatment because of the irregular control of glycosuria and the tendency to severe hypoglycemic reactions. The use of protamine zinc insulin in this group has been less encouraging, and satisfactory control can only be obtained in a small percentage of cases with a single dose of protamine zinc insulin. The general consensus, however, is that the results are superior to those obtainable with regular insulin.

The latent period of soluble insulin varies from fifteen minutes to one hour and its maximum duration of action four to six hours. Protamine zinc insulin begins to exert its maximal action after three hours and this action may be prolonged from twenty-four to forty-eight or even seventy-two hours. Regular insulin is therefore best adapted for the control of postprandial hyperglycemia and glycosuria. Because of its limited time of action it will be of little value in the control of the increasing nocturnal hyperglycemia which characterizes the severe diabetic. Protamine zinc insulin liberated at the rate of 3 to 4 per cent an hour from its subcutaneous deposit will control the nocturnal and fasting hyperglycemia but will not be available in amounts adequate for the hyperglycemia that follows meals. It should be emphasized that the primary objective of treatment with protamine zinc insulin is the control of the disease during the night. Experience has demonstrated that this can be best accomplished by a single dose of protamine zinc insulin one hour before breakfast. The maximum effect on the blood sugar is exerted twenty to twenty-four hours after its administration. By administering protamine zinc insulin before breakfast, it is therefore possible to utilize a single specimen of urine, that passed before breakfast, as a reliable guide to dosage. If the specimen before breakfast is sugar-free for three to four days, a blood sugar determination should be made regardless of the degree of postprandial glycosuria. Under no circumstances should the

dose of protamine zinc insulin be increased to control the postprandial glycosuria in the presence of a normal fasting blood sugar level. Such a procedure may result in serious hypoglycemic reactions. Furthermore in establishing the dosage of protamine zinc insulin, changes in diet and medication should only be made after three or four days as there is reason to believe that protamine zinc insulin may exert a cumulative effect for as long as seventy-two hours.

With the dose of protamine zinc insulin established by the fasting urine specimen and blood sugar level, a persistent postprandial glycosuria can be controlled by one of two methods: (1) by supplementary doses of regular insulin or (2) by modifications of diet. The supplementary use of regular insulin means multiple injections and in this way one of the main advantages of protamine zinc insulin is lost. However multiple injections may be necessary in those cases that cannot be adequately controlled by dietetic methods. It has been our experience that protamine and soluble insulins cannot be combined in the same syringe as protamine zinc insulin contains an excess of protamine that will partially precipitate the soluble insulin.

Our experience has agreed with that of Wilder, Joslin, Campbell<sup>1</sup> and others that better control is usually obtained if not more than 150 grams of carbohydrate are included in the daily allowance. Others have reported satisfactory results with as much as 300 grams of carbohydrate daily but in most cases the disproportion between the insulin available and the large carbohydrate intake at meals creates difficulty in control. After all, the usual diet of 150 grams of carbohydrate (70 of protein and 80 of fat) permits three slices of bread, a large portion of oatmeal, three portions of fruit, four portions of 5 per cent vegetables, one-quarter pint each of milk and cream, an egg, two moderate portions of meat and three portions of butter.

The usual difficulty in treating the severe diabetic with protamine zinc insulin is the tendency to postprandial glycosuria, especially after breakfast, and the tendency to hypoglycemia during the night and in the early morning. The most common method of overcoming postprandial glycosuria is to spread the meals, withholding portions of carbohydrate for afternoon and bedtime feedings. To overcome marked fluctuations in the blood sugar level we have attempted to regulate the diet so as to retard the absorption of glucose and in this way prevent the flooding of the blood and tissues with sugar after meals. By this method

we have hoped to strike a more even balance between the glucose available for oxidation and the insulin liberated from its subcutaneous depot Dr Pollack<sup>2</sup> has demonstrated that carbohydrates differ in their relative rates of availability as glucose. This is especially true of fruits. For all practical purposes fruit juices represent almost pure glucose solutions which are rapidly absorbed and cause a sharp rise in the blood sugar. On the other hand, such a fruit as the banana is slowly absorbed and produces a less marked elevation of blood sugar. The addition of fat in the form of heavy cream to fruits and cereals delays the emptying of the stomach and retards still further the absorption of glucose thereby prolonging its availability. The advisability of a small breakfast is suggested by the common tendency to glycosuria after this meal.

The problem of avoiding nocturnal and early morning hypoglycemia requires a constant supply of glucose during the night. It is known that from 50 to 60 per cent of protein is convertible into glucose and that the emptying time of the stomach after a meat meal may be as long as three hours. For protein to become available as glucose it must be digested, the amino-acids carried to the liver, deaminized and resynthesized into glucose. The time necessary for these processes prolongs the availability of the glucose derived from protein. This suggests the advisability of a large meat meal at night and the serving of the evening meal as late as possible. In accordance with these observations we have adopted the following dietetic regime for use with a single dose of protamine zinc insulin administered before breakfast:

- 1 Diets are limited to 150 grams of carbohydrate at the onset
- 2 The use of readily absorbed fruits and fruit juices is avoided
- 3 Carbohydrate is divided into  $1/5$ ,  $2/5$ , and  $2/5$  for breakfast, lunch and supper
- 4 Proteins are divided into  $1/6$ ,  $1/6$  and  $2/3$  for breakfast, lunch and supper

With this regimen we have usually been able to avoid the necessity of supplementary feedings and to control the tendency to nocturnal hypoglycemia.

However, in spite of all dietetic methods an appreciable postprandial glycosuria frequently develops in the presence of a normal or even sub-normal fasting blood sugar level. At times the glycosuria will appear and disappear for no detectable cause. More often the cause will be found in errors of technique in the administration of protamine zinc insulin. To

evaluate a case properly the history of the actual vial of insulin used must be known. Many jobbers and retail druggists keep the protamine zinc insulin on the open shelves of a hot storage room for a variable period of time with consequent damage to the insulin. Even if the patient who buys the insulin is as careful as possible the damage has already been done. In addition the storage of insulin on the window sill, the small gauge needle, the droplet of alcohol accidentally put into the insulin vial and the hot syringe may contribute to failure in therapy. The frequent development of subcutaneous indurations at the site of the injections suggests that irregular absorption may also be an important factor. A varying percentage of cases, however, cannot be controlled with protamine zinc insulin according to the usual standards. There is no doubt that a fair proportion of patients taking protamine will not be as nearly sugar-free throughout the twenty-four hours as when taking three or four doses of regular insulin a day.

This raises the important question of the criteria for adequate control. These range from the insistence upon a normal blood sugar throughout the day to the other extreme that no attempt should be made to restrict the diet or control glycosuria but to administer protamine in doses adequate to prevent ketonuria. It may be possible to prevent hyperglycemia throughout the twenty-four hours by the administration of soluble insulin before each meal in addition to protamine zinc insulin in the morning. However in the majority of even moderately severe cases an attempt to maintain a normal blood sugar throughout the day will result in frequent hypoglycemic reactions. Joslin<sup>3</sup> has recently stated that the restriction of the loss of sugar in the urine to 10 per cent of the carbohydrate in the diet is justifiable. According to the dietary regime used by Joslin and the average urinary excretion, this approximates 11 per cent glycosuria. We have considered a fractional glycosuria after meals with no more than an occasional trace of sugar in the urine before breakfast as satisfactory control. In evaluating standards of control, a distinction must be made between the glycosuria which follows a meal and that which occurs during the night. The former represents an overflow from an exogenous food supply, the latter is derived from the stores of glycogen and the breakdown of endogenous protein. There are periods during the twenty-four hours when the tissues of the severe diabetic treated with insufficiently frequent doses of unmodified insulin deliver amino-acids for the manufacture of dextrose. This results in recurring periods of negative



nitrogen balance and an accompanying ketosis Wilder<sup>1</sup> has demonstrated that even in the presence of an appreciable postprandial glycosuria, the endogenous production of glucose and the resulting protein wastage can be prevented by protamine zinc insulin. Furthermore, the absence of ketosis during the twenty-four hours is much more complete with protamine zinc insulin than was ever possible with three or even four doses of soluble insulin in cases of severe diabetes. The nitrogen sparing and anti-ketogenic effect made possible by the continuous action of protamine zinc insulin is the basis for the relaxation of standards of diabetic control and the abandonment of a consistently sugar-free urine as the essential aim of diabetic therapy.

One of the fundamental concepts of diabetic therapy has been that an uncontrolled glycosuria increases the susceptibility to the untoward complications of diabetes. This is especially true of the young diabetic where the clinical picture is not complicated by senile degenerative changes. In the adult, tissue susceptibility in the presence of glycosuria is probably best illustrated in infections which remain refractory to treatment until the diabetes has been controlled. Coma has in large part been eradicated as a cause of diabetic mortality and our therapeutic problem today is the prevention of the degenerative changes to which the diabetic is particularly susceptible. It may be that with the prevention of acetonuria and protein wastage, the degree of glycosuria is of no significance in the production of degenerative changes. The cause of these degenerative changes is not known and the evidence that hyperglycemia and glycosuria are etiological factors in their production is not convincing. Eventually we may be able to state that glycosuria with protamine zinc insulin is not harmful because there is always functioning insulin in the body, a status not attainable with soluble insulin. However, even though a continuous supply of insulin is available and protein wastage and acetonuria can be prevented by protamine zinc insulin, the prevention of degenerative changes in diabetes is far too serious to be dismissed with the assumption that a persistent glycosuria is harmless without more convincing evidence than has as yet been presented.

The most serious complication encountered in the use of protamine zinc insulin is the hypoglycemic reactions. These are especially malignant in that the hypoglycemia develops gradually and is not attended by the stormy symptoms characteristic of regular insulin. If the patient is confined to bed or is resting, symptoms may be entirely absent or appear

late It is a common experience to encounter a patient completely symptom free in spite of a blood sugar of 30 or 40 mgms When symptoms appear they are characterized by drowsiness, fatigue, headache and nausea They are often overlooked at the onset, especially as they may occur at a time when the patient cannot believe that the initial warning symptoms are of hypoglycemic origin Because of the slow fall in blood sugar the compensatory mobilization of epinephrin is less pronounced and the tremor, sweats, tachycardia and throbbing sensations that characterize the reactions with regular insulin do not appear Furthermore, the hypoglycemia may recur after treatment or even after meals Sugar should therefore be administered at half hour intervals for a prolonged period and should be immediately resumed if symptoms recur Because of the absence or paucity of symptoms and the danger of insulin reactions with protamine zinc insulin, patients should not be dismissed from observation if the fasting urine contains no sugar unless the blood sugar has been determined Another important factor to be borne in mind is the hypoglycemic effect of muscular exercise in the presence of protamine zinc insulin Most of the severe reactions which have been reported have followed undue exertion It is therefore necessary to regulate the amount of physical activity and to administer carbohydrate before and after exercise to neutralize the depressing effect of exertion on the blood sugar Furthermore, there is experimental evidence to indicate that severe prolonged hypoglycemia may produce permanent pathological changes in the central nervous system

There is usually no difficulty in starting ambulatory patients on protamine zinc insulin but the transfer of patients long accustomed to regular insulin to protamine zinc insulin may be associated with serious difficulties One of the few cases of coma that we have seen during the past year was precipitated by the abrupt transfer of a moderately severe diabetic from regular to protamine zinc insulin without the use of supplementary doses of soluble insulin It does not seem that the difficulties encountered can be entirely explained by the fact that the full effect of protamine zinc insulin is available only after seventy-two hours In the light of my personal experience, I do not believe that a severe diabetic should be transferred from regular to protamine zinc insulin without hospitalization

In the preoperative and postoperative care of surgical diabetics and in the treatment of diabetic acidosis and infections protamine zinc

insulin has proved of value. Protamine zinc insulin can be given with comparative safety several hours before an operation for by the time it becomes effective the need for it will have arisen. One-half to two-thirds of the usual dose may be given on the morning of the operation. Any glycosuria that may develop after the operation can be controlled by regular insulin. The daily use of protamine zinc insulin, supplemented if necessary by regular insulin, can be continued during the postoperative period until the patient is ready to resume his regular regime. Protamine zinc insulin may also be used in the treatment of diabetic acidosis and coma. The patient may be given a large dose of protamine zinc insulin at the beginning of treatment and regular insulin then administered for the next three or four hours as though the protamine zinc insulin had not been given. Similarly, in infections the patient may be given his usual maintenance dose of protamine zinc insulin to be supplemented by regular insulin as indicated by fractional urine specimens.

Other modified insulins have been suggested for the treatment of diabetes during the past two years. It has been demonstrated that certain basic amines, histones and other substances in combination with zinc will increase the effectiveness of insulin. There is no doubt that the chemical and physical properties of insulin determine its physiological action. In difficult cases neither unmodified nor protamine zinc insulin completely solve our problem. Perhaps after continued investigation and experimentation modified insulins may be developed to solve any diabetic problem. However, the so-called "tailor-made insulin" belongs to the future. For the present we are limited to regular and protamine zinc insulin.

#### SUMMARY

At the end of two years, certain conclusions may be drawn as to the value of protamine zinc insulin. Its prolonged action makes available a constant supply of insulin throughout the day and night. Unfortunately, it is not a substitute for the normal pancreas as the insulin is liberated from its subcutaneous depot at a constant rate rather than in response to the physiological demands of the body. Protamine zinc insulin has undoubtedly facilitated the treatment of the mild and moderately severe diabetic previously controlled by thirty units or less of regular insulin. It has not solved the problem of the severe diabetic. Perhaps 25 per cent of these cases may be satisfactorily controlled with a single dose of protamine zinc insulin. Another 25 to 50 per cent may be controlled with

the aid of supplementary doses of unmodified insulin. In the remaining cases it has been possible to control the nocturnal glycosuria but it has not been possible to keep the urine sugar-free during the day without the precipitation of serious hypoglycemic reactions. Unfortunately there are no criteria by which one can predict which cases will respond satisfactorily to protamine zinc insulin.

A distinction must be made between postprandial and nocturnal glycosuria in that the latter is derived from stored glycogen and endogenous protein. There is therefore reason to believe that the glycosuria after meals which is not associated with protein wastage or acetoneuria is less harmful than that which occurs in the intervals between periods of activity of unmodified insulin. It is our opinion that this demonstrated ability of protamine zinc insulin to prevent protein wastage and ketonuria justifies its use in severe diabetics even if no more satisfactory control of the glycosuria can be attained than by repeated injections of soluble insulin. It would be unfortunate if this were interpreted to mean that control of glycosuria is no longer the essential aim of diabetic therapy.

There is no doubt that the use of protamine insulin requires greater care on the part of both the physician and the patient. The utmost care in the technique of administration and dietetic management which balances available insulin with available glucose will be necessary if satisfactory results are to be obtained. As other observers have pointed out, protamine zinc insulin has improved but has not simplified the treatment of diabetes.

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## LIBRARY NOTES

## RECENT ACQUISITIONS

A legacy, recently acquired by the Library from the estate of the late Dr. Lawrason Brown fills a gap on our shelves with one of the truly great works in the history of medicine. It is unnecessary to dwell at length on a book so often described and praised as "the first record of the use of immediate percussion of the chest in diagnosis," Leopold Auenbrugger's *Inventum novum ex percussione thoracis humani*. Vienna, 1761. It is with great satisfaction that we add this to our collection.

One of the most rare and interesting works which we have acquired in some years is an early English work translated from the French, the *Questionary of chirurgiens with the Formulary of Iytell Guido in chirurgia with the fourth booke of the therapeutike or methode curatylfe of Claude Galien*.

London, 1541. It appeared in French in 1533 with the title, *Questionnaire des chirurgiens et barbiers avec le formulaire du petit Guidon*. The text relates that the *Questionnaire* follows that which the master surgeons and barbers of Montpellier used in testing those being examined in the art of surgery. Parts of it seem to be abstracts of excerpts from the great work on surgery of Guy de Chauliac. It is of particular interest as it demonstrates the little knowledge required by a surgeon in the years preceding the advent of Paré. With it is the *Formulary* of Guy de Chauliac, originally published in Latin with the title *Chirurgia parva* in the late fifteenth century. Nicaise maintains that it is very doubtful if this is the work of Guy de Chauliac, but some parts of it seem to be taken from his work. It is strange that although the text of Guy de Chauliac's surgery was translated into English not long after it was written (as our manuscript attests), yet it was not published in that language, so that the only printed English version to

bear the name of that great surgeon is this little *Formulary*.

It may be of interest to quote from the preface to the volume written by Henry Copland, the translator: "Gentyl reders in consideration that every science, arte, and faculte that are speculate & practised by philosophers, not onely ought to be shewed and taught unto suche as be present with them in their dayes, but also for a perpetuall benefyte to be set forth by wrtyng in vulgarly in every tongue, for the more credence and cruedition of all yonge and pregnant practicers, as fayne wolde attayne to the perfumens of every suche science, arte, and faculte. And not withstandinge that there be right many and sondry sortes, as well of very good and scientyke bookes, as of right expert men within this realme in the seventyeall arte of chirurgery. Nevertheless this lytell questionary & formulary with the other bookes added therto have been often requyred and soughte for, to be had in englysshe (as well of me as of other) by divers and many persones of the sayde science. A certayne yonge gentyl man enured in the sayde science have a booke of the same in frenche moved the right honest persone Henry Dabbe bibliopolyst & stationer to have it translated in to englysshe. At whose instygacion meanyng the help of God (though moste rudely) with the symplence of a good wyllyng herte I have enterprised to do it in folowinge directly my copy."

In the history of medicine few figures are remembered for more outstanding achievements than the Italian physician, Marcello Malpighi, 1628-1694, whose fame rests on valuable contributions to anatomy, biology, histology, embryology and physiology. The Library has now acquired his work on another subject in two handsome folio volumes published by the Royal Society of London,

entitled *Anatome plantarum Cui subiungitur appendix, iteratas & auctas ejusdem auctoris De ovo incubato observationes continens*

London, 1675-1679, containing many full-page engraved plates. I can do no better than to quote from W. G. MacCallum's excellent article on Malpighi in the *Johns Hopkins Hosp Bull*, August, 1905:

"It would be impossible to enter into the details of Malpighi's enormous work which concerns especially phanerogams, but also some pteridophyta, fungi, galls, and parasitic plants. Hooke had seen plant cells and regarded them as merely cavities partitioned off from the general cavity. Malpighi, however, made a distinction between cells and fibers and vessels. With rare perspicacity he saw that all plants are composed of a complex of sacs or vesicles which constitute the fundamental tissues, and these he called otricoli. The generalization of this principle manifests the synthetic power of his mind. He had thus arrived at the modern distinction between parenchyma and prosenchyma, further than which he could scarcely go without a knowledge of protoplasm and the possibilities in the modification of cells.

His recognition of the continuity of leafstalks, branches, stem, and roots, and of the fact that the floral envelopes and cotyledons are modified leaves brought him very near to the ideas of Wolff and Goethe that all the diverse plant products may be traced from a few single types.

He described minutely with drawings of sections studied microscopically the wood and bark, the medullary rays, the tracheid vessels, scalariform and pitted vessels, sclerenchyma and woody fibers, the medulla, the nature of the annual rings, and so on, but erred in ascribing the origin of the wood fibers to the bast. From watching the growth of many plants he concluded that there was an essential difference between those which grew with one cotyledon only and those which started with two and thus divided as we now divide them, the phanerogamous plants. Not only this but he recognized that there is a fundamental difference in the arrangement of the fibro-vascular bundles which corresponds with this division.

Most of his studies were, however, not merely morphological but sought to explain the physiology and laws of development of plants. Malpighi probably did not actually see the fertilization in the flower. Nevertheless, his work on the development of the ovum into the seed and of the ovary into the fruit and then of germination of the seed is classic.

He recognized the need of air for plants, and again with his zoophysiological ideas ascribed the function of carrying the air to the tracheids.

Of his *De ovo incubato*, and his *De formatione pulli in ovo* Garrison says that the plates accompanying it make him the founder of descriptive or iconographic embryology, surpassing all other contemporary workers on the subject in the accurate notation of such minutiae as the notochord, the heart, the neural groove, the cerebral and optic vesicles.

It may be of interest to note that in vol. I the letters are printed which passed between Malpighi and Oldenburg of the Royal Society in the years 1671 to 1675. See Birch's *History of the Royal Society*, vols. II and III for references to the correspondence which led to the publication of this work by that Society. The first mention appears on p. 499 of vol. II as follows: "Mr. Oldenburg produced and read a letter of Signor Malpighi, dated at Bologna Nov. 1, 1671, and accompanying a manuscript containing an abstract of his observations and considerations of the structure of plants which, he said, he intended to enlarge and to illustrate with figures, if he should find, that the Society approved of his attempt." On p. 179 of vol. III it is reported at the meeting of Jan. 21, 1675, that Mr. Oldenburg produced the manuscript of the work itself with a letter from Malpighi of August 20, 1674. On June 17, 1675, the Council met and ordered that it be published. The license was granted on June 24. The second volume which appeared in 1679, was presented to the Society December 5, 1678 whereupon the Society ordered that it be printed.

## A SELECTED LIST OF PERIODICALS ADDED IN 1938

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Chicago, Vol 1, No 1, Jan 1938
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"Possession does not imply approval"

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BULLETIN OF  
THE NEW YORK ACADEMY  
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MAY 1939

THE DIAGNOSTIC SIGNIFICANCE OF  
CHANGES IN THE RED CELLS\*

RUSSELL L. HADEN

**A** NORMAL man always has about twenty-five trillion red cells in the circulating blood. The cells are remarkably uniform in size, shape, and hemoglobin content. All the erythrocytes together make up the erythron, which is best thought of as a vessel holding hemoglobin. The erythron normally varies little in volume since the number and size of the red cells and the total blood volume are quite constant. The characteristic biconcave shape of the erythrocyte is a most efficient one because it combines adequate capacity for containing hemoglobin with favorable conditions for the rapid diffusion of oxygen.

An adult male weighing 150 pounds has (Fig. 1)

- 1 A total blood volume of about 5 liters
- 2 A total red cell mass or erythron of over 2 liters which holds about 700 gm. of hemoglobin
- 3 Five million biconcave cells per c. mm.
- 4 A mean red cell volume of 90 cubic microns
- 5 A mean cell hemoglobin content of 30.8 micromicrograms
- 6 A mean cell hemoglobin concentration of 34.2 per cent.

\* Delivered October 28, 1938, in the Eleventh Annual Graduate Forum,  
From the Cleveland Clinic, Cleveland, Ohio.

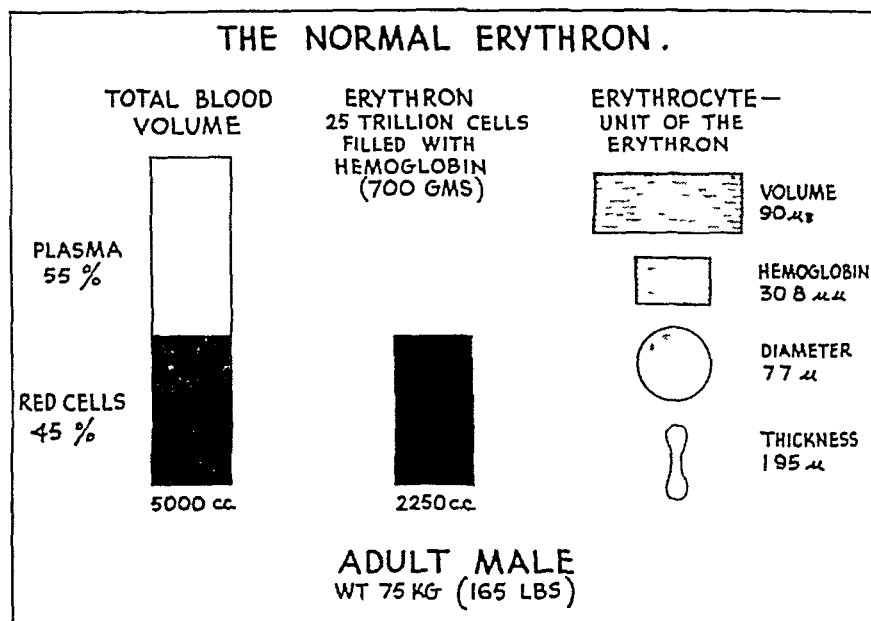


Fig 1—The normal erythron The erythron is the total mass of red cells The unit of the erythron is the erythrocyte

7 A mean cell diameter of 7.7 microns

8 A mean cell thickness of 1.95 microns

The cells normally in the circulation are mature as shown by the absence of nuclei and nuclear remains and by reticulation and basophilia in only a small percentage The erythrocyte may vary in total mass, number, size, shape, hemoglobin content, and maturity

The sole purpose of the red cell is to transport oxygen which it is enabled to do by reason of its hemoglobin content Each cell is fully saturated or filled with hemoglobin and functions like a cup on an endless chain conveyor (Fig 2) The hemoglobin is constantly taking up oxygen in the lungs and constantly releasing it in the tissues The hemoglobin in the erythrocyte is really outside the blood plasma It thus exerts no osmotic pressure and so does not disturb the normal balance between tissue fluids and plasma

The total red cell mass or erythron has received little attention Normally the total blood volume varies only in relation to body weight so the red cell mass calculated from the total blood volume and hematocrit reading is quite constant (males, 30 cc, females, 27 cc per kg).

## THE FUNCTION OF THE RED CELL

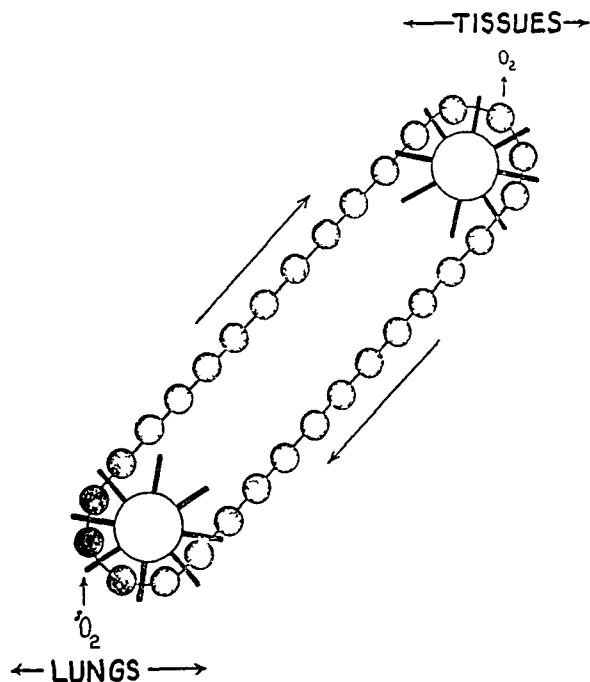


Fig 2—The red cell functions as a cup on an endless chain conveyor. The cup (erythrocyte) is normally filled with hemoglobin which takes up oxygen in the lungs and gives it up in the tissues.

With an anemia the hematocrit value decreases (Fig 3) while the total blood volume usually remains unchanged so the mass of erythron may fall to a very low level. The total blood volume is seldom significantly increased except in polycythemia vera where it is always greater than normal. The hematocrit value is also constantly increased in this condition, so the total red cell mass and the mass per kg are always large. I have observed the volume of the erythron as high as 8000 cc in polycythemia vera and as low as 400 cc in aplastic anemia (normal 2000-2500 cc). The determination of the total red cell mass is of diagnostic value only in polycythemia where it helps greatly in differentiating polycythemia vera from the symptomatic type. In symptomatic polycythemia the amount per kg is not significantly increased even with a marked increase in red cells per c mm<sup>1</sup>.



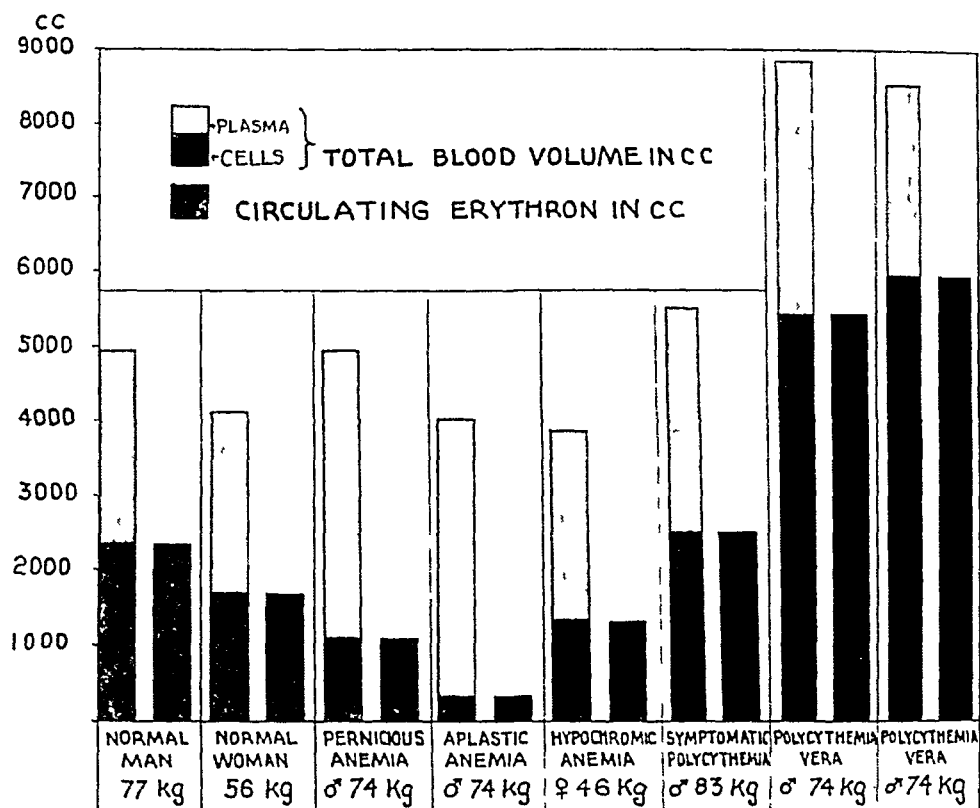


Fig 3—The circulating erythron as determined from total blood volume and hematocrit readings varies greatly in the blood dyscrasias

The erythrocyte, the unit of the erythron, is constantly changing. New red cells are formed and old cells are disposed of at a rapid rate. An erythrocyte lives only three to four weeks, so about a trillion cells are destroyed and replaced daily. The stages through which every red cell must pass are summarized in Table I. The bone marrow may be visualized as a grist mill (Fig 4) into the hoppers of which the materials to make new red cells are constantly being fed.<sup>2</sup> A stream of new erythrocytes is constantly pouring into the circulation to replace the old cells removed by the spleen. To make new cells, two specific substances, iron and the erythrocyte maturing factor (EMF) supplied by liver and liver substitutes, are necessary as well as the basic substances present in all cells. The only recognizable remains of the red cells are bilirubin and iron, which are formed as end-products of hemoglobin destruction. Iron, the inorganic element necessary for the formation of hemoglobin, is the only

TABLE I

LIFE HISTORY OF THE ERYTHROCYTE

SUBSTANCES necessary for all cell life and growth

ENDOTHELIAL CELL → MEGALOBLAST

Factors necessary for change unknown

MEGALOBLAST → NORMOBLAST

Erythrocyte maturing factor (EMF) in  
liver and liver substitutes necessary for  
change

Some multiplication at megaloblast stage

NORMOBLAST → RETICULOCYTE → MATURE ERYTHROCYTE

Multiplication most active at normoblast  
stage

Iron necessary for normal division and  
growth of normoblast and formation of  
hemoglobin

MATURE ERYTHROCYTE → BLOOD STREAM

Lives two to six weeks in circulation

Dies by fragmentation and is engulfed by  
reticulo endothelial cells largely in the  
spleen

End products

Iron

Bilirubin

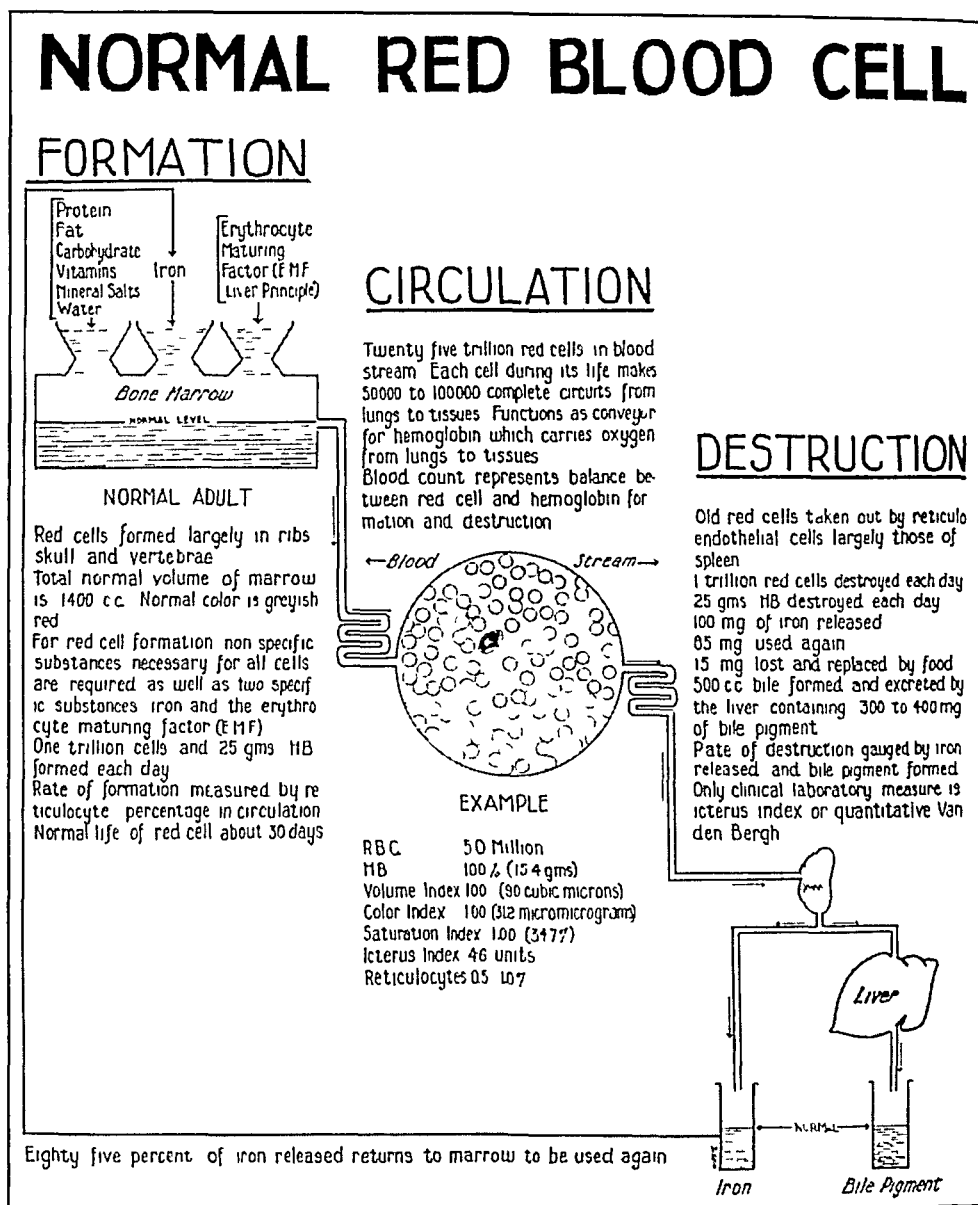


Fig 4—The physiology of the normal red cell. A cell lives about thirty days so about one trillion cells and 25 grams of hemoglobin are destroyed and formed every day.

constituent known to be used over and over.

Certain laboratory studies are necessary to detect variations in the red cell. These are relatively simple and can be carried out accurately (Fig 5). The exact total red cell mass is calculated from the total blood volume and the hematocrit reading. The total blood volume is normally so con-

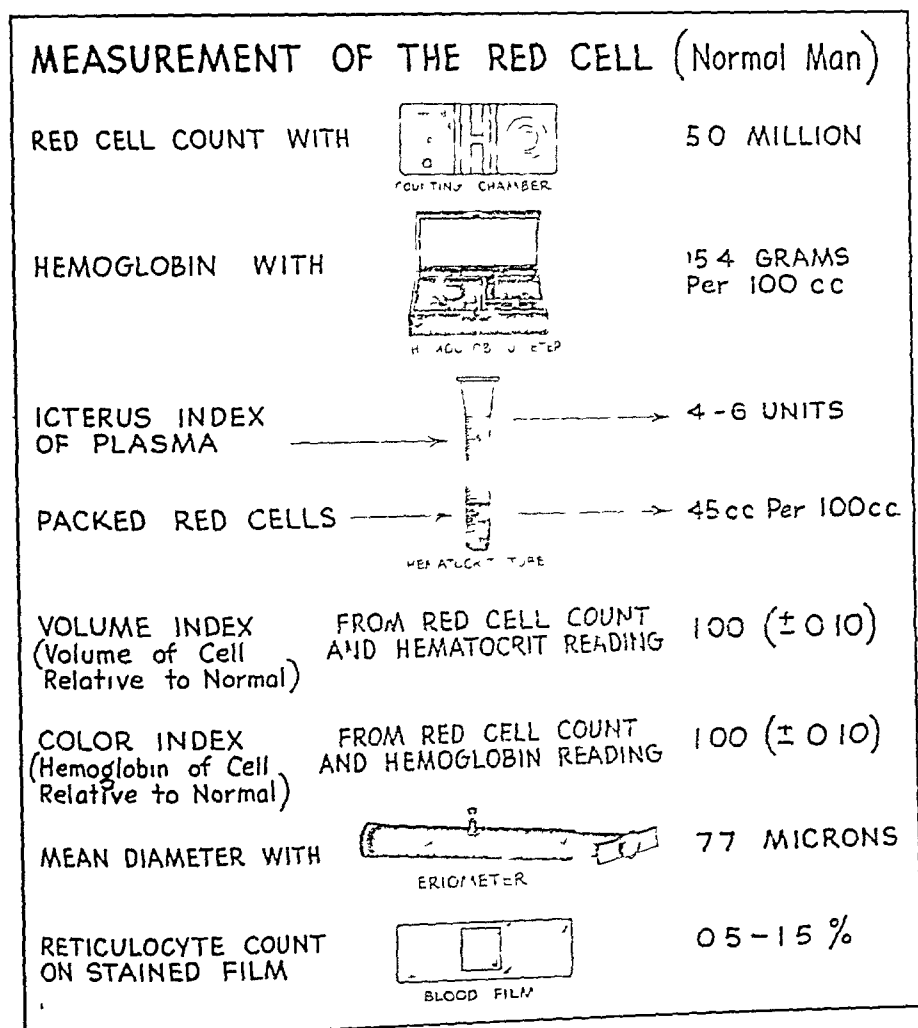


Fig 5—The measurement of the number, volume, hemoglobin content, and diameter of the red cell is simply done. The icterus index measures the rate of red cell destruction and the reticulocyte count the rate of release of new cells into the circulation.

stant that it seldom needs to be measured except in polycythemia. In all cases the hematocrit reading, the hemoglobin, the red cell count, the bilirubin content of the plasma, and the percentage of reticulocytes are determined. Blood films are studied to detect qualitative changes and for measuring the mean diameter of the erythrocytes. The technique for such a blood study has been discussed fully elsewhere.<sup>3</sup>

The necessary determinations are made as follows

- 1 *Red cell count* done in the usual manner
- 2 *Hematocrit reading* in cubic centimeters obtained by centrifuging a measured amount of blood mixed with an isotonic coagulant From the red cell count and hematocrit reading are figured
  - a The *mean cell volume* in cubic microns
  - b The *volume index* which records the mean cell volume relative to normal
- 3 *Hemoglobin* in grams From the red cell count and the hemoglobin are calculated
  - a The *mean cell hemoglobin* content in micromicrograms
  - b The *color index*, which records the mean cell hemoglobin relative to normal
- 4 *Icterus index* as a measure of the bilirubin by comparing the color of the plasma with a standard solution of potassium bichromate
- 5 *Reticulocyte count* on a film stained with brilliant cresyl blue
- 6 *Mean cell diameter* measured by a diffraction method
- 7 *Examination of a stained film* for qualitative changes in cells

In recording the volume and hemoglobin content of the mean cell, the volume index and color index which express the findings relative to normal are preferred The mean cell volume and mean cell hemoglobin are absolute figures but indicate nothing except in comparison with the normal This relation is shown directly by the volume and color indices

Instead of measuring the mean cell diameter only, a distribution curve (Price-Jones) which records the variation in diameter of cells may be determined by measuring the diameter of a large number (500 or more) of cells (Fig 6) This procedure is very time-consuming The volume of the cell is a much more sensitive indicator of a change in size than is the diameter, however, since it records thickness as well as diameter A 14 per cent increase in diameter corresponds to a 40 per cent increase in volume if the thickness is increased equally with the diameter In certain instances the diameter may be increased even with a decrease in volume or decreased without a corresponding change in volume If the anisocytosis is marked, the base of the distribution curve is wide but the type of distribution curve is of no special clinical significance Since the mean cell volume is so easily determined and is such a sensitive indicator of any change in cell size, we much prefer this to the distribution curve (Price-Jones)

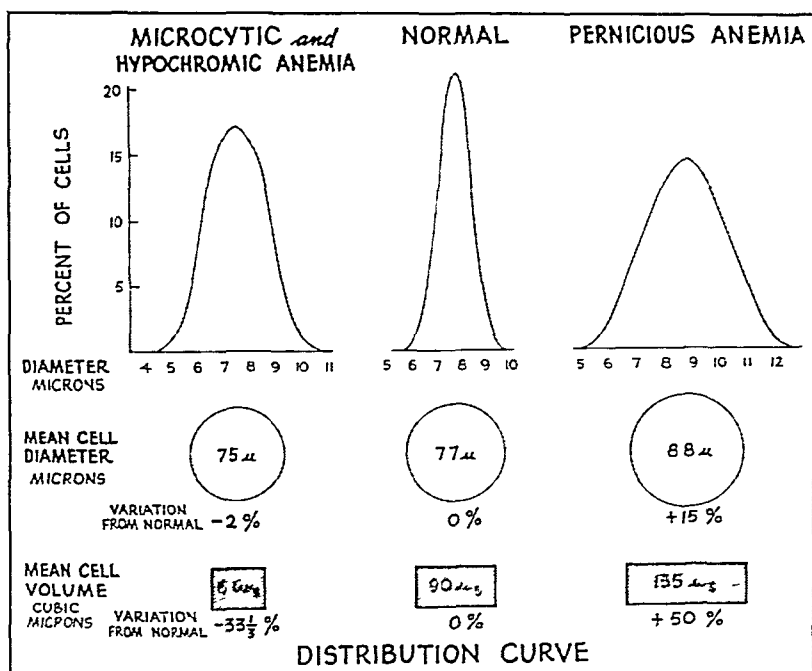


Fig 6—Distribution curves (Price-Jones) of the red cell. These show the degree and anisocytosis by the spread of the curve as well as the mean diameter. The change in volume is much greater than the change in diameter, however.

The mean cell thickness may be important in relation to the diameter. This is calculated with the aid of a three-dimensional chart from the mean volume and the mean diameter.

After the exact state of the red cell is determined as outlined, what application is to be made of the data? The first and most important use is to classify the anemias. The only satisfactory laboratory classification is based on the size and hemoglobin content of the mean red cell. On this basis there can be only six different types of anemia (Fig 7). They are

- 1 *Normocytic and normochromic*. The mean cell has a normal volume and hemoglobin content. Volume index and color index, 1.00 ( $\pm 0.10$ ) [Fig 7, 1]
- 2 *Normocytic and hypochromic*. The mean cell has the normal volume but is incompletely filled with hemoglobin and so has less than the normal quota. Volume index 1.00 ( $\pm 0.10$ ) and color index,  $< 1.00$  [Fig 7, 2]

## TYPES OF ANEMIA

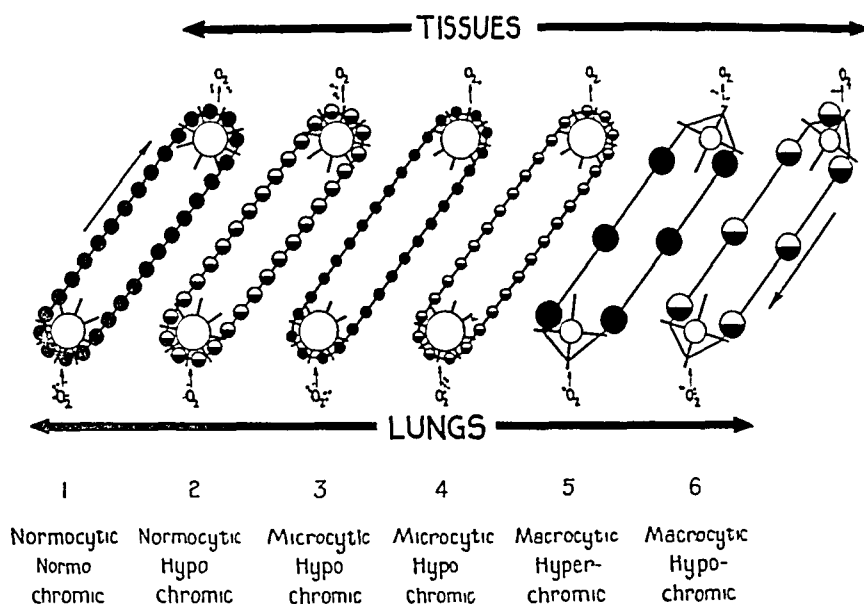


Fig 7—Types of anemia represented as varying kinds of endless-chain conveyors

- 3 *Macrocytic and hyperchromic* The mean cell has a volume larger than normal and more than the normal amount of hemoglobin. Volume and color index,  $> 1.00$  [Fig 7, 5]
- 4 *Macrocytic and normochromic* The mean cell is larger than normal but contains a normal amount of hemoglobin although the concentration is less than normal. Volume index,  $> 1.00$ , and color index  $1.00 (\pm 0.10)$  [Fig 7, 6]
- 5 *Macrocytic and hypochromic* The mean cell is larger than normal and contains less than the normal quota of hemoglobin. Volume index,  $> 1.00$  and color index,  $< 1.00$  [Fig 7, 6]
- 6 *Microcytic and hypochromic* The mean cell is smaller than normal and contains less than the normal amount of hemoglobin. Volume and color index,  $< 1.00$  [Fig 7, 3 and 4]

An accurate study of the red cell also affords necessary information concerning the cause of an anemia. An anemia is only a loss of balance between red cell formation and red cell destruction. An erythrocyte

TABLE II

CLINICAL CLASSIFICATION OF ANEMIA

- I Increased blood loss
  - A Mechanical loss from hemorrhage
  - B Accelerated red cell destruction by
    - 1 Hemolytic agents (as phenylhydrazine or bacterial toxin)
    - 2 Rapid red cell removal from an abnormality of cell shape (as congenital hemolytic icterus), overactivity of reticulo-endothelial system, or defect in cell structure
- II Decreased blood formation
  - A Quantitative decrease in red marrow from aplasia as in benzol poisoning, or crowding out of erythrogenic tissue as in leukemia or myeloma
  - B Quantitative depression of marrow activity as by malignancy, hypometabolism, chronic toxemia such as nephritis or cachexia
  - C Qualitative decrease in marrow activity from deficiency of specific substances necessary for normal marrow activity
    - 1 Deficiency in supply, absorption, or use of erythrocyte maturing factor (EMF) as in pernicious anemia or sprue
    - 2 Deficiency in supply, absorption, or use of iron as in chronic hemorrhage, dietary lack, and idiopathic hypochromic anemia

count shows nothing but the relation between these two phases of the red cell. In clinical hematology it is necessary to know the rate at which cells are being formed and destroyed and the basis for the loss of balance producing an anemia or polycythemia. A lack of cells and hemoglobin may be due either to an increased destruction or to a decreased formation of cells. The most logical clinical classification of anemia is based on these two fundamental factors, increased red cell loss, and decreased red cell production. A clinical classification of anemia based on this method of production is shown in Table II.

The number of red cells per c mm gives no clue concerning the rate of new cell formation or of loss of cells. It does record the balance at the time the count is done. The reticulocyte level shows the number of young cells in the circulation. If there is an excessive number of reticulocytes, new cells are being released from the marrow in abnormally large numbers since the reticulation persists in the cell after reaching the circulation for only a short time. It is apparent that the marrow must be hyperactive if many new cells are being released. On the other hand if the reticulocytes are below normal in an anemia red cells are not being released from the marrow. This may be due to hypoplasia or to underfunction of the



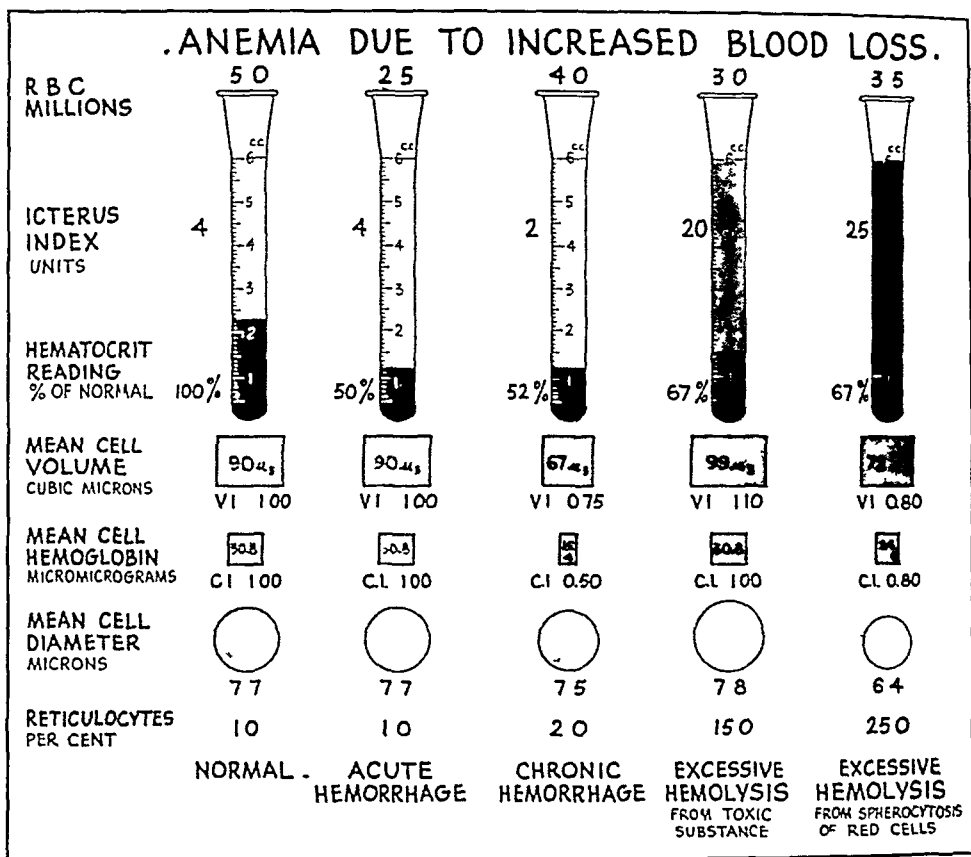


Fig 8—The anemias due to increased blood loss. If the blood loss is due to chronic hemorrhage, the icterus index is low and the cells are small and deficient in hemoglobin, if due to increased hemolysis, the cells tend to be larger, the reticulocyte count is elevated, and the icterus index is higher.

ciency of hemoglobin there is a hypochromia or low concentration in the cell and if a low hemoglobin content continues the cell decreases in size. This microcytosis seems to be due to the fact that the sole function of the cell stroma is to hold hemoglobin. If hemoglobin is lacking the cell becomes smaller since there is no use in having stroma if there is no hemoglobin to transport. A hypochromia of the red cell as shown by the low color index or a microcytosis as shown by the low volume index thus indicates a deficiency in iron.

The anemias due to decreased red cell formation are shown in Fig 9.

Rarely both the erythrocyte maturing factor (EMF) and iron are

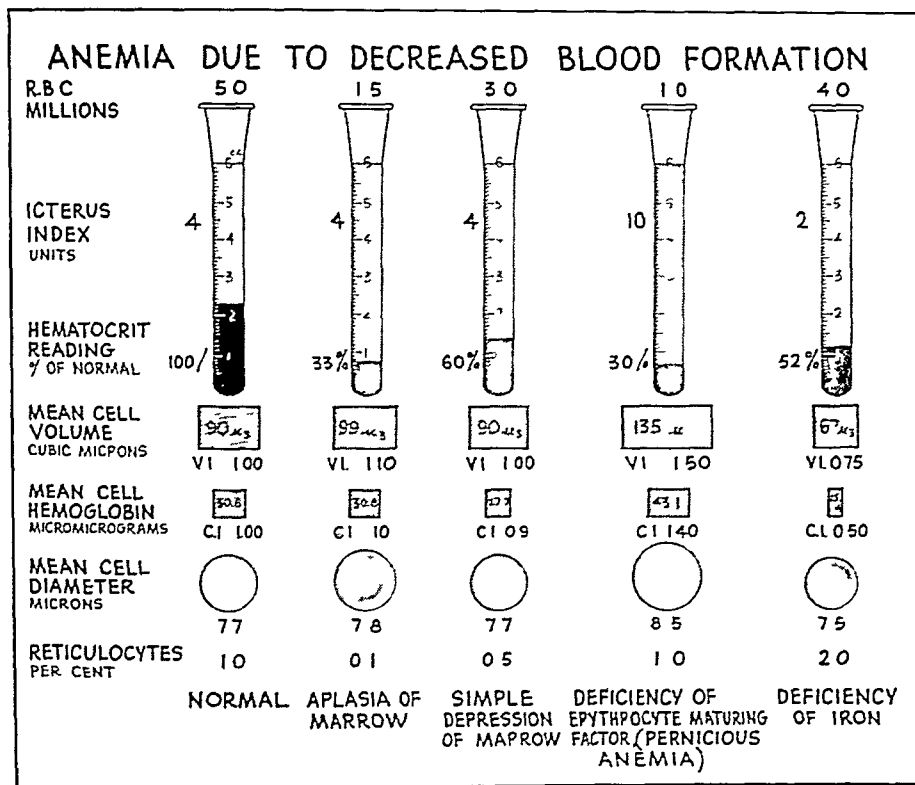


Fig 9—The anemias due to decreased blood formation. If the decreased blood formation is quantitative, the mean cell varies little from normal, if due to a deficiency in building materials, the mean cell is small with a lack of iron and large with a lack of the erythrocyte maturing factor supplied by the liver.

deficient. Since a lack of the erythrocyte maturing factor (EMF) produces a macrocytosis and a lack of iron, a microcytosis, the algebraic sum of both deficiencies may result in a cell of normal size.

Wherever there is a disordered erythropoiesis, the shape of the cell may be disturbed. Thus in pernicious anemia due to a lack of erythrocyte maturing factor (EMF) or an iron deficiency anemia the cells are not only small or large but may also be abnormal in shape. Such a variation or poikilocytosis has no significance except to indicate a marked disturbance in red cell formation.

The most interesting abnormalities in the shape of red cells are the congenital variations. While the cell is normally a biconcave disk, the

prevailing cell may be globe-, oval-, or sickle-shaped. These shapes represent congenital anatomic malformations similar to a steple-skull, the absence of iris pigment, or a patent interventricular septum. Such cells function just as efficiently as biconcave disks but are taken out of the circulation more rapidly than new cells can be formed, so, an anemia usually results.

The almost constant anemia of congenital hemolytic icterus is due to the characteristic globe cell or spherocyte. This peculiarly shaped cell is the congenital abnormality of the disease. The shape of the cell may show all variations from the normal biconcave disk to a true sphere. The fragility varies directly with the degree of spherocytosis. A red cell before hemolyzing in a hypotonic salt solution assumes the spheroid form. If the cell tends to be normally spheroid it is apparent that it is already on the way to hemolysis, so hemolysis becomes complete in a much less hypotonic solution of sodium chloride than with cells of normal shape. The spleen seems "tuned" to the normal cell, the biconcave disk. When cells of an abnormal shape come to it, they are quickly filtered out. Normally these are only the disintegrating cells. In sicklocytosis, ovalocytosis, or spherocytosis, the abnormally shaped cells are rapidly removed from the circulation just as old cells are. The length of life of the erythrocyte when the shape is abnormal may thus be only a few days as contrasted with the normal three to four weeks. The anemia of congenital hemolytic icterus thus results from the shape of the cells and not from the increased fragility. The fragility may be correlated directly with the degree of spherocytosis.<sup>4</sup>

Red cells may become larger from conditions other than a deficiency of the erythrocyte maturing factor (EMF) although this is the most common cause. With a marked reticulocytosis, the mean cell is nearly always somewhat increased in volume because reticulocytes as young cells are larger than mature erythrocytes. Likewise in a true aplastic anemia where the red cell formation reverts to a primitive level, the mean volume increases. It is not uncommon to find a macrocytosis in nutritional deficiency disease other than pernicious anemia. Thus in sprue and pellagra the mean cell volume may be increased. Here, however, this finding may be due to a lack of erythrocyte maturing factor (EMF) or some interference with its use.

In cirrhosis or other diseases of the liver, large red cells are frequently present. In cirrhosis there is usually a true macrocytosis as shown by an

increase in volume The determination of mean red cell volume may be a valuable measure of liver function It has not been proved whether this macrocytosis is due to a disturbance in storage of the erythrocyte maturing factor (EMF) and so an insufficient supply to the marrow or to the fact that the liver in some way enters into the utilization of the erythrocyte maturing factor (EMF) There is also another characteristic change in red cells in relation to liver disease With simple obstructive jaundice the red cell almost always increases in diameter without changing in volume Here the erythrocyte is a much flattened biconcave disk Such a cell is more resistant to hemolysis than is a normal cell and returns to normal shape when the biliary obstruction is relieved

Small red cells or microcytosis may result from an exhaustion of the marrow from any cause Some microcytes are present in almost every type of serious anemia The most important cause for a microcytosis, however, is a defect in supply or utilization of iron, so, less hemoglobin than normal is present With the deficient supply of hemoglobin there is no need for stroma to contain it The total mass of stroma falls usually by decreasing the volume of the mean cell As a rule the number of cells per c mm changes little With a microcytosis there is almost always a lower concentration of hemoglobin in the red cells as the diminution in mass of stroma seldom equals the decrease in hemoglobin A hypochromia of the red cells is common even with an adequate supply of iron Many factors, such as infection, toxemia, or hypometabolism may prevent the proper utilization of iron by the marrow cells and so produce a hypochromia A hyperchromia in the sense of an increased concentration of hemoglobin per unit volume of cell is impossible since stroma cannot be supersaturated If the cells are large, more than the normal quota can be carried in each cell due to the increase in volume of stroma

Accurate data on the red cell also helps greatly in treating the anemias A macrocytosis usually indicates a deficiency of the erythrocyte maturing factor supplied by liver In treating pernicious anemia the primary indication is to supply the missing factor continuously in adequate amount When adequately supplied, the macrocytosis of the red cells disappears as shown by the return of the volume index to normal If a macrocytosis persists, the treatment is incomplete When liver therapy is first instituted in an active untreated case of pernicious anemia, there is a tremendous outpouring of reticulocytes or young cells which are completed by supplying the erythrocyte maturing factor These are

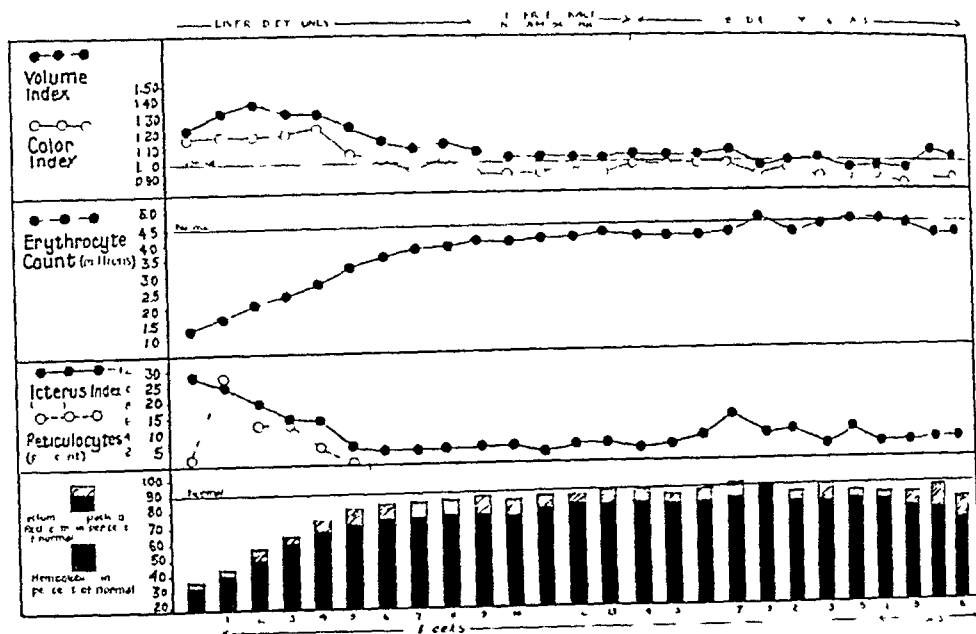


Fig 10—The red blood cell in pernicious anemia with adequate liver therapy. The volume index is high before treatment and returns to normal. So long as the treatment is adequate the volume index remains normal.

usually larger than normal so the volume index may rise for a time with the reticulocytosis. The icterus index quickly falls showing that the cells are no longer dying abnormally in the marrow because they cannot be completed. Soon the red cell count, the hemoglobin, and the volume index return to normal (Fig 10). The purpose of treatment is to have them remain so. Long before any clinical symptoms arise as a result of the disease, deficiency in the needed factor may be detected by a rise in the volume index.

The course of an iron deficiency anemia may also be followed by determining the volume index and color index. The characteristic low volume index and color index rise to normal if iron is adequately supplied and is used by the marrow (Fig 11).

Other qualitative changes in erythrocytes such as basophilia and nucleation have little significance. These only indicate the marrow activity of which the most sensitive indicator is the number of reticulocytes.

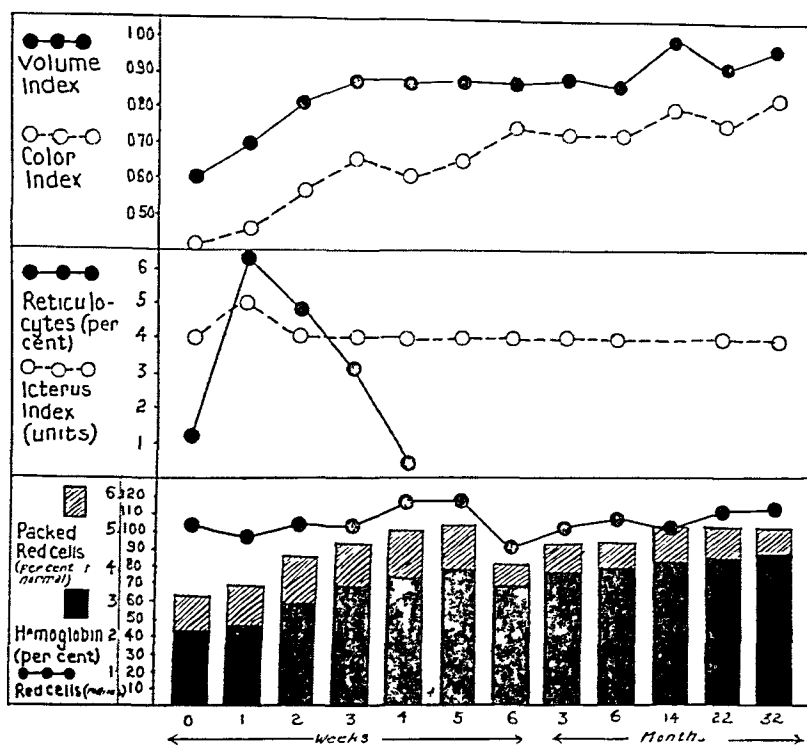


Fig 11—The red blood cell in an iron deficiency anemia. Here the mean cell is small as indicated by a low volume index and is deficient in hemoglobin (low color index). With adequate iron therapy, the volume and color indices gradually rise while the red cell count changes little.

## SUMMARY

In every blood dyscrasia an accurate study of the red cell is necessary. This study should routinely include:

1. Red cell count
2. Hemoglobin estimation
3. Hematocrit reading
4. Mean cell diameter
5. Volume index as measure of mean cell volume
6. Color index as a measure of mean cell hemoglobin content
7. Stained film for reticulocyte count, basophilia, nucleation, and abnormalities in shape
8. Icterus index

Exceptionally we need also

- 1 Total blood volume
- 2 Total red cell mass
- 3 Distribution curve (Price-Jones) of cell diameter
- 4 Calculation of thickness

An increase in red cell mass per kilogram of body weight occurs only in polycythemia vera, a decrease occurs in all anemias

The red cell count and hemoglobin show only the balance between blood formation and destruction at the moment the test is made

The icterus index measures the rate of hemoglobin destruction and thus indirectly of red cell loss

The reticulocyte count measures the rate of release of red cells from the marrow, and thus indirectly records the activity of the marrow

A deficiency of erythrocyte maturing factor (EMF) is shown by a macrocytosis, a deficiency of iron is shown by a hypochromia or microcytosis

The volume and hemoglobin content are the best indicators of (1) the lack of the specific maturing factor supplied by liver and by iron, and (2) the adequacy of supply of these factors in an anemia due to such a deficiency

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## POLYCYTHEMIA\*

PAUL REZNIKOFF

## INTRODUCTION AND CLASSIFICATION

POLYCYTHEMIA means an increase in red blood cells per unit volume of blood above a value which is considered normal. There are many causes for this state but whether the exact etiology is apparent in any given case or not, it is clear that the more knowledge we have about polycythemia, the more probable it is that all polycythemic states are either secondary or overcompensatory mechanisms to some general or local physiological or pathological change, rather than primary conditions.

While many classifications of polycythemia exist, probably the simplest is the division into two groups, suggested by Harrop and Wintrobe<sup>1</sup>—a mild type which might be called erythrocytosis, similar to leukocytosis, and the pronounced state or erythremia, analogous to leukemia. From a physiological viewpoint polycythemia may be (a) relative, as seen in conditions in which there is a loss of plasma, (b) transient, such as occurs after splenic contraction, and (c) absolute, when the total cell mass as well as the total blood volume shows a sustained and pronounced increase.

Erythrocytosis need concern us little in this discussion. It is seen in a variety of conditions and circumstances, such as congenital heart disease, mitral stenosis, pulmonary arteriosclerosis, at high altitudes, secondary to the action of many chemicals, and after hemorrhage.

Erythremia,<sup>2</sup> however, presents a distinct clinical picture and has been known by various names, as polycythemia vera, or polycythemia rubra. It is instructive in reviewing a disease to go back to original papers and see how much progress has really been made since a pathological concept was first described. In 1892 Vaquez<sup>3</sup> definitely claimed that polycythemia was due to hyperactivity of the hematopoietic organs, and

\* Delivered November 2, 1938 in the Eleventh Annual Graduate Fortnight.  
From the New York Hospital and Department of Medicine, Cornell University Medical College.



in 1903 Osler<sup>4</sup> established all the cardinal evidences of this condition—cyanosis, polycythemia, and splenomegaly. It is also interesting to note that of his own four patients, one was a Russian Jew and one a Turkish Jew. In his 1908 paper<sup>5</sup> he suggested that anoxemia was the important pathological mechanism responsible for polyglobulism and mentioned the possibilities of x-ray therapy. These ideas are probably the most important features of polycythemia as we know it today.

### ETIOLOGY

Many causes have been proposed to explain the etiology of erythremia. That a familial or hereditary type exists is generally accepted. The reports of Engelking<sup>6</sup> and of Spodaro and Forkner<sup>7</sup> give two excellent descriptions of this form. An outstanding feature of the familial, as contrasted with the ordinary type, is the fact that the individuals who have hereditary polycythemia rarely suffer from the severe symptoms of the disease. While an endocrine factor has been suggested because of the erythrocytosis in cases of pituitary basophilism,<sup>8</sup> hyperthyroidism, and suprarenal tumors, in most of these latter conditions the increase in erythrocytes rarely reaches the degree found in the ordinary type of polycythemia. Occasionally splenic tuberculosis and thrombosis of the splenic vein may also be characterized by an elevated red cell count, but these conditions are rare. A neoplastic conception of the cause of polycythemia is not generally accepted because of the absence of abnormal cells and the lack of invasiveness. A few reports<sup>9, 10, 11</sup> have been published of cerebral lesions inducing erythremia, such as injury to the proximal part of the vegetative brain centers, or diseases like encephalitis. Morris'<sup>12</sup> conception that polycythemia is due to excess secretion of a gastric substance, addisin, has not been verified by most workers.

This disease is most prevalent in males in middle or late life and there seems to be a preponderance among Jews born in Eastern Europe. This can be illustrated by a study of six institutions<sup>13</sup> in which the incidence of erythremia in this group was about 48 per cent contrasted with less than 10 per cent of general admissions. Such a finding naturally suggested an analogy to thromboangitis obliterans and induced us to investigate the blood vessels of the bone marrow. It is important to make such studies on the bone marrow of subjects whose blood counts have approached normal by therapy to avoid excessive congestion of the bone marrow vessels which tends to make the vasculature scarce and, even in normal tissue,



Fig 1—Artery in bone marrow of normal subject. Magnified  $\times 280$ . Practically no fibrous tissue infiltration of wall of vessel.



Fig 2—Artery in periosteum of arteriosclerotic patient. Magnified  $\times 280$ . Fibrous tissue infiltrating muscularis.

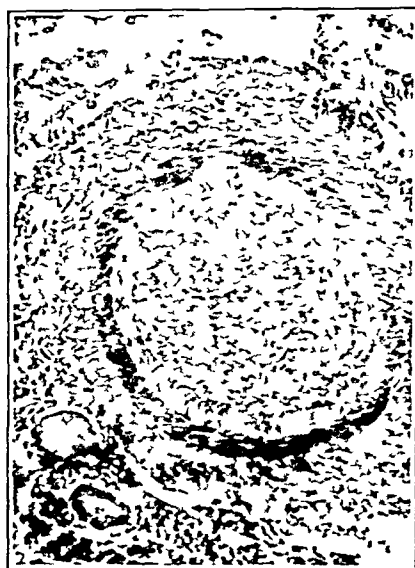


Fig 3—Artery in bone marrow of a polycythemic patient. Magnified  $\times 110$ . Marked fibrosis of subintima and adventitia.

TABLE I

RACIAL AND NATIONAL ORIGIN OF PATIENTS SUFFERING  
FROM POLYCYTHEMIA VERA

Institutions	Total No of patients (polycy- themia vera)	Patients of Jewish origin born in eastern Europe (polycythemia vera)		General admission of patients of Jewish origin born in eastern Europe Per cent
		No	Per cent	
Bellevue Hospital	28	14	50	3 (sample year)
Cornell Clinic	7	4	57	12 (estimate)
New York Hospital	19	12	63	9 (sample year)
Presbyterian Hospital	33	13	39	15 (race not given, east- ern European birth)
St Luke's Hospital	34	15	44	7 (race not given, east- ern European birth)
New Haven Hospital	13	6	46	10 (estimate)
	134	64	47.8	9 (approximate)

difficult to visualize. It is also essential to use a Masson trichrome stain to bring out the fibrous tissue adequately. Under such conditions it was found that in polycythemia the capillaries are markedly thickened and that in most cases the arteries and arterioles show adventitial and sub-intimal fibrosis. What causes such lesions is not known but it is of interest that in one early case the bone marrow showed inflammatory lesions along the course of the vessels. These observations have led us to propose the theory that erythremia may be due to local anoxemia in the bone marrow itself, with overcompensation of erythropoiesis. Since the lesion is local, the failure to lower the blood count by subjecting a patient to oxygen therapy is easily understood. Whatever the cause of polycythemia, all workers are agreed that the increase of erythrocytes in this condition is not due to decreased destruction or prolonged longevity of the red blood cells but is primarily dependent upon a heightened production.

### PATHOLOGY

At autopsy the vessels are found to be engorged, hemorrhages and thromboses are common, the spleen and liver are large and hyperemic, and sometimes cirrhosis is seen. The marrow of the long bones is engorged and that of the short bones frequently is characterized by erythroblastosis and leukoblastosis. Increase of megakaryocytes is usual.

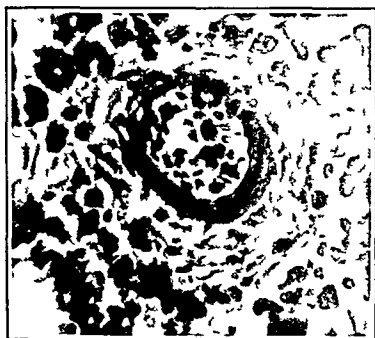


Fig 4—Arteriole in bone marrow of normal subject Magnified  $\times 270$  No fibrosis in wall of vessel

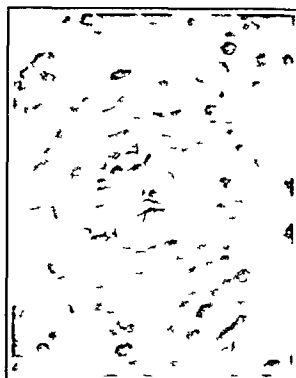


Fig 5—Arteriole in bone marrow of polycythemic patient Magnified  $\times 540$  Fibrous tissue infiltrating entire wall of vessel

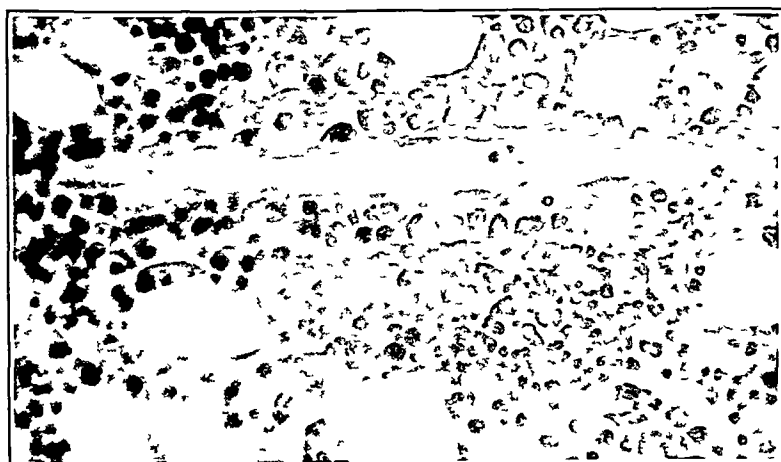


Fig 6—Capillary in bone marrow of normal subject Magnified  $\times 270$  Thin wall nuclei bulging into lumen

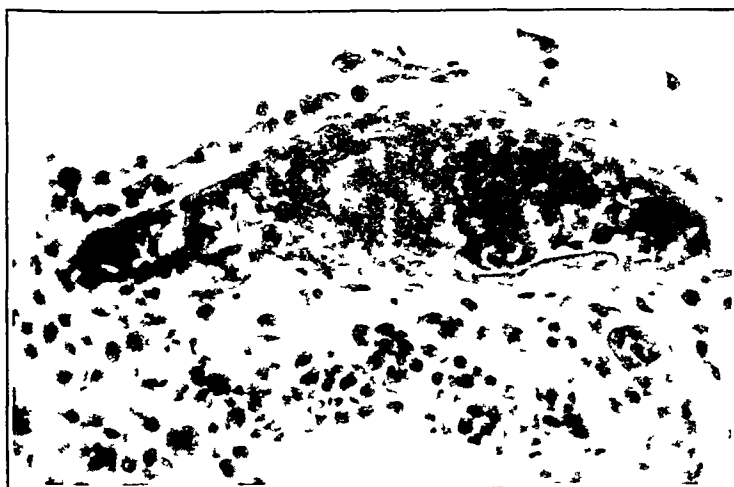


Fig 7—Capillary in bone marrow of polycythemic patient Magnified  $\times 200$  Marked thickening of wall Cross section of markedly thickened small capillary in field

## SYMPTOMS AND SIGNS

The symptoms and signs of polycythemia are too well-known to require detailed description. The skin and mucous membranes show a cyanosis which is reddish blue, with dilated superficial vessels. Bleeding is not uncommon from the nose and gums, and these patients usually have bloodshot eyes. Erythromelalgia and skin eruptions occur occasionally. Clubbed fingers are usually absent in true polycythemia, but are seen in the familial type and in erythrocytosis secondary to heart and lung lesions.

Cardiovascular changes are common, especially arteriosclerosis, thrombosis, varicosities, and phlebitis. While true cardiac hypertrophy is rare, the x-ray picture usually shows some increase in heart size. Cardiac decompensation is a late phenomenon. Except for the Gaisbock type of polycythemia, which is really a nephrosclerosis, the blood pressure is only slightly elevated if at all.

Many of the symptoms of polycythemia are related to the nervous system. Usually patients complain of headache, dizziness, and a sense of fullness of the head. Paresthesias and pruritis are common. Vascular accidents in the fundi may cause blindness and the engorged tortuous vessels of the deeply colored retina explain the frequency of visual disturbances. Many complications involving the nervous system are due to the slowing of circulation of the cerebral vessels causing anoxemia<sup>14</sup>. While these occurrences may be transitory, actual thromboses and hemorrhages of the cerebral vessels may produce serious accidents. The average polycythemic patient is depressed and has a sluggish mentality. However, these individuals frequently demonstrate a combination of mental activity and irritability which makes them exceedingly uncomfortable household companions. It must be remembered that even when therapy has brought the blood count to normal, these nervous phenomena may persist and suggest that some of the disturbances are really due to vascular changes rather than to a polycythemia itself.

Many patients complain of pain and fullness in the left upper quadrant due to splenic enlargement, and constipation and flatulence are common. Gastrointestinal hemorrhages and thromboses produce a serious complication in erythremia. Cirrhosis of the liver may occur in the course of polycythemia and this lesion is explained on the basis of long continued congestion. One of the most interesting problems involving the gastrointestinal tract is the relationship of erythrocytosis to duodenal ulcer<sup>15</sup>.

Many of these patients do not have hyperacidity and although thrombosis of the vessels or erosion of distended vessels have been considered as causative factors, many workers now believe that the increase of erythrocytes, which is usually moderate, in many cases of duodenal ulcer is due to bone marrow overcompensation for low grade bleeding

About three-fourths of all polycythemic patients have splenomegaly This is not present in the Gaisbock type The engorgement of the spleen may lead to infarcts and perisplenitis and cause severe pain

Hirsch<sup>16</sup> has found nodules by x-ray examination of the lungs which he thinks may be subpleural thrombi or small hemorrhages These disappear in about three weeks

#### LABORATORY FINDINGS

The hematopoietic system has received much attention in this disease The average red blood cell count in untreated patients varies between 8 and 12 million per c mm, and the hemoglobin, which is normal in function, ranges between 18 and 24 gm per 100 cc of blood The cells are usually normocytic, occasionally microcytic Reticulocytes average between 1 and 2 per cent Polychromatophilia, basophilic stippling, and even nucleated red blood cells may be found but the factor of hemorrhage or treatment by hemolytic agents must be considered when these immature forms are prevalent Leukocytosis, polynucleosis, increase in immature polymorphonuclear cells, and thrombocytosis are usual Tendency to hemorrhage is supposed to be due in part to poor clot retraction because of increase in cellular mass and decrease in serum It is important, therefore, to undertake surgical procedures, such as dental extractions, with great care and to insist upon the hospitalization of the patient The viscosity of the blood may be five to eight times normal and the specific gravity varies between 1.075 and 1.080, compared to the normal of 1.055 to 1.065 The sedimentation rate is greatly retarded Haden<sup>17</sup> has recently emphasized the importance of determining the total red blood cell mass in diagnosing polycythemia This is greatly increased since the total blood volume may be in some cases almost twice the normal, the hematocrit is markedly increased, and therefore the total cell mass may approach a three-fold rise

Certain features concerning the hematological complications of polycythemia merit consideration The relationship of this disease to leukemia has often been described and in fact some believe that there is a definite

disease entity known as erythroleukemia in which both diseases coexist. Others think that erythremia may terminate as a definite leukemia and still another group does not accept these concepts but holds that early in leukemia there may be an irritation of the contiguous erythrogenous bone marrow, giving an increase in red blood cell count. Whatever the true explanation of so-called erythroleukemia may be, it is not difficult to conceive of the contiguous irritation theory as one compatible with our knowledge of the bone marrow. Certainly the leukogenic and thrombocytogenic tissue shows evidence of stimulation in most cases of polycythemia, and this should afford no more surprise than does leukocytosis and thrombocytosis following acute hemorrhage.

Some polycythemic patients finally develop anemia and others thrombocytopenia with purpura. An exhaustion hypothesis has been proposed to explain these phenomena and this also fits in with the theory of the end result of prolonged anoxemia. However, it is important in such complications to be sure that one is not dealing with the final picture of prolonged depression therapy, either x-ray or chemical.

A few miscellaneous observations may be itemized. The basal metabolic rate may be increased. Whether this is due to increased formation of red blood cells or an increase in uric acid is not known. However, it is interesting to note that gout has frequently been reported complicating polycythemia.<sup>18</sup> The blood flow is slow, the skin capillaries distended, the respiratory minute volume is increased, and the vital capacity reduced. Albuminuria is usually present.

### THERAPY

It is not possible to review in detail all the methods which have been used to treat polycythemia. Therefore, this paper will deal principally with the four types of therapy used most commonly: venesection, acetylphenylhydrazine, irradiation, and Fowler's solution.

Venesection, removing 500 cc. of blood as often as twice a week, has in its favor the rapid amelioration of symptoms such as dizziness and headache. Recent work has shown that such a procedure produces very little bone marrow stimulation.<sup>19</sup>

Acetylphenylhydrazine, in doses of 0.1 gm. daily or every other day, until the blood count begins to fall and thereafter a maintenance dose, is well tolerated by most patients. This drug is not only hemolytic but apparently has some depressing action on the bone marrow. In using

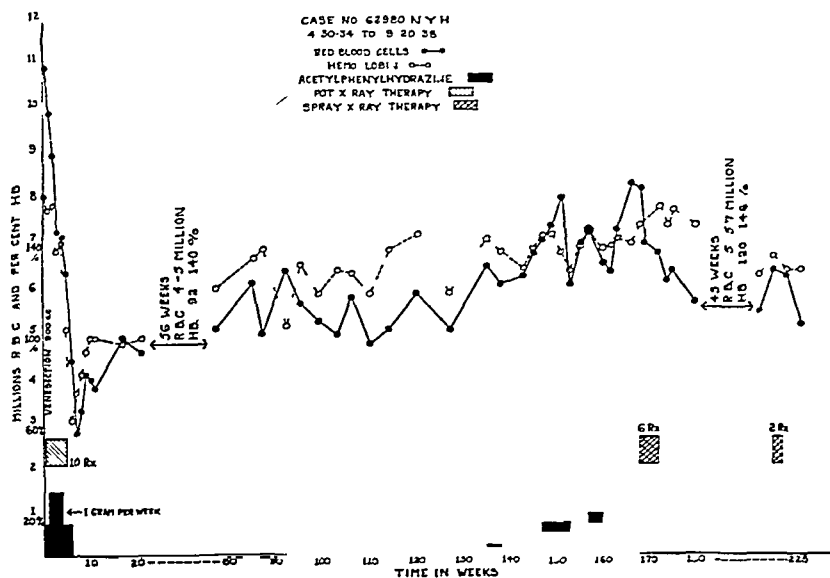


Fig 8

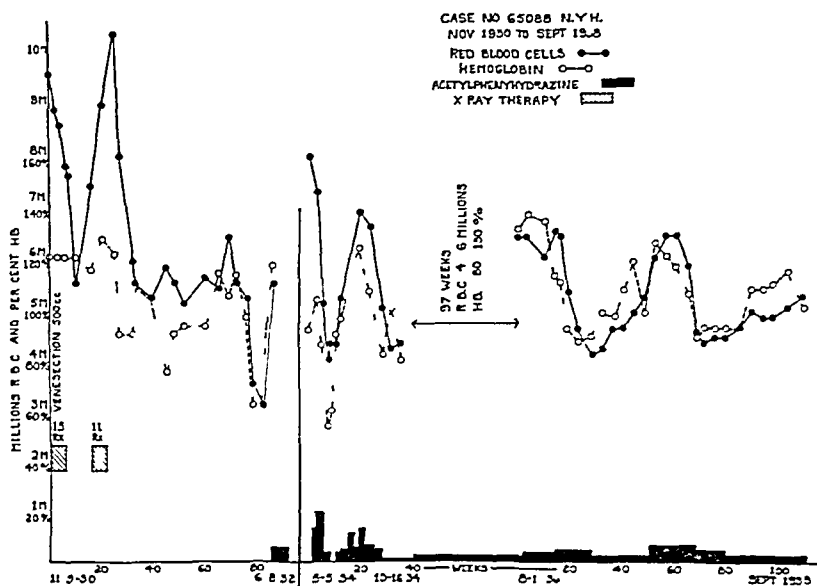


Fig 9

Figs. 8, 9—Course of polycythemia treated with venesection, acetophenylhydrazine and irradiation





The diet should exclude condiments, too much roughage, alcohol, and foods and liquids which are very hot, as all of these may irritate the already congested gastrointestinal mucosa. Above all, it is important to keep the patient's blood count at a level which gives the greatest comfort and least complaint, rather than reach some arbitrary base line on a chart. The physician must not treat a blood count but the entire patient.

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## CHRONIC GASTRITIS\*

RUDOLF SCHINDLER

I **I**N THIS paper I shall confine myself strictly to the discussion of primary chronic nonspecific gastritis. After death the gastric mucosa disintegrates so rapidly that usually post-mortem changes can only be recognized by gross and microscopic inspection. Therefore, the diagnosis of chronic gastritis was thoroughly discredited. Only when it became possible to observe the living gastric mucosa through the gastroscope was the frequency and importance of this disease rediscovered and described. Even so, the anatomic foundation of chronic gastritis is uncertain. We do not know very well the histology of the normal stomach of the adult. Material obtained at gastric resection does not give indisputable evidence of the preoperative condition of the stomach, as will be shown later. The normal gastric mucosa of the newborn is better known, it differs from that of adults, and there has been the tendency to make the microscopic diagnosis of chronic gastritis in every adult because of this fact. This is not permissible. There certainly are findings which are the remnants of the frequent acute gastritides of childhood, there is the physiological response of the gastric mucosa to the daily irritation by coarse, hot or cold food. These are the physiological changes the gastric mucosa undergoes. If we should call them pathological, then no adult would have a normal gastric mucosa, and such a definition cannot be accepted.

However, changes are sometimes found which evidently are proof of a disease. In the more severe cases we cannot doubt that a serious gastric disease is present. There is atrophy, the glands have disappeared, there is infiltration, and the epithelium has undergone a metaplasia into intestinal epithelial type, many goblet cells are seen. Such pronounced changes, however, are rarely seen histologically. The pathologist is usually unable to decide whether a gastritis exists or not.

The gastroscopic picture of gastritis is more easily recognized, as I shall endeavor to show you. Gastroscopic examination can be easily carried out repeatedly in healthy and in sick people. If the proper tech-

\* Delivered January 5, 1939 at the Annual Meeting of The New York Academy of Medicine  
From the Department of Medicine, The University of Chicago

nique is used, the patient does not experience any considerable discomfort and, therefore, we are able to examine many patients once a week up to thirty, or even sixty-five, times. Thus we can study normal and diseased stomachs at repeated examinations. The picture obtained by our modern, flexible, safe gastroscope is brilliant and sharp. It permits the visualization of much finer detail than even the inspection of the gross specimen. It is always amazing to see how difficult it is to find a small ulceration in the gross specimen, a lesion seen so readily at gastroscopy. This difference is due to the blood circulating at gastroscopy, absent in the gross specimen.

My conclusions regarding the gastroscopic appearance of the normal stomach were based on a study of healthy people of all age groups.<sup>1</sup> The gastric mucosa of the healthy adult looks smooth, and at the ridge of the folds, glistening, silk-like, it contains high-lights, its color is a uniform orange-red. It should be emphasized that older people also, up to sixty or sixty-five years of age, show the same picture, and we should dismiss the idea that at this age atrophic processes are frequent.

If we examine gastroscopically patients suffering from abdominal distress we often find pictures which differ from those found in healthy people. In almost 50 per cent of these patients we find diffuse alterations. The mucosa may show red patches and layers of adherent, glary, grayish mucus. Such red patches have been described by Beaumont in his famous observations made at the gastric fistula of his servant, Alexis St. Martin, and it is interesting to note that all the changes observed so beautifully by Beaumont and disregarded so entirely for a hundred years, now are rediscovered at the gastroscopic examination. Sometimes the secretion may even be purulent. Histologic checks are rare. However, I obtained the unique microscopic picture of a very outspoken superficial gastritis observed gastroscopically. At a laparotomy a biopsy was taken without the use of any clamps, microscopic sections revealed tremendous superficial infiltration by plasma cells.

If we watch the course of this type of gastritis, which I have called "chronic superficial gastritis," over a period of months or years, two different types of the course are observed. Either the changes disappear, the patient becoming entirely healthy, or chronic atrophic gastritis develops. In some areas of the stomach the signs of superficial gastritis are still seen, in adjacent portions, however, the mucosa becomes thin, mottled, grayish or greenish-gray in color. Atrophy may be patchy, or

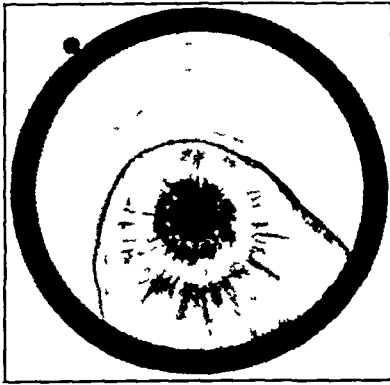


Fig 1 a

Fig 1, a and b

*Gastrosopic (a) and microscopic (b) picture of the normal gastric mucosa*  
 Gastrosopically the normal mucosa is smooth, silk-like View of antrum, angulus and pylorus—The microscopic section demonstrates the mucosa of the body of the stomach Only few interstitial cells are seen

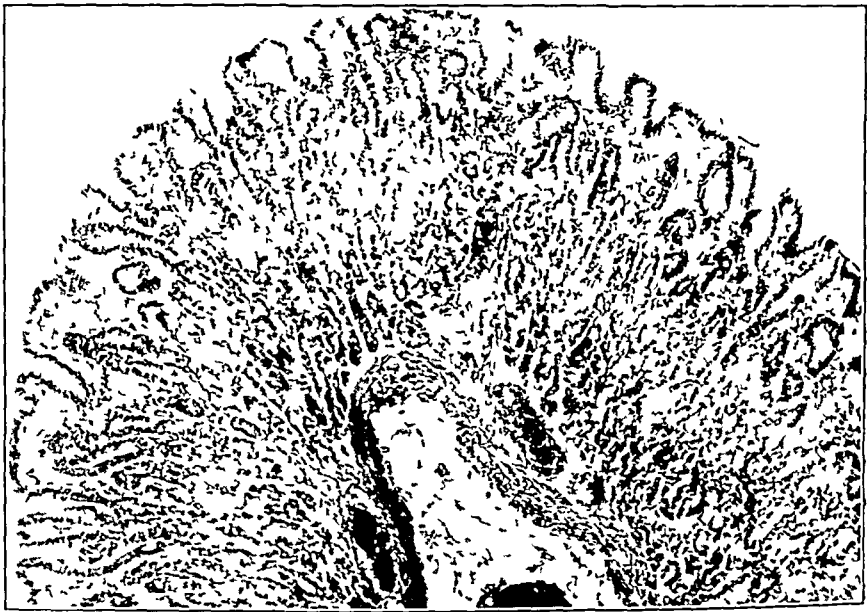


Fig 1 b

more diffuse, or complete Blood vessels, always absent in the normal mucosa, are seen Here the question comes up whether such a condition may still be called inflammation, or do we have to deal with a merely degenerative process However, this atrophy so often develops from an inflammation We do not know if there are cases at all without preceding inflammation, nor do we know whether the inflammatory process is entirely gone In cases of deficiency states, as in pernicious anemia, the first thing we can see gastrosopically is superficial gastritis Brown has

seen definite inflammatory changes histologically in pernicious anemia, Jones and Benedict<sup>2</sup> observed hypertrophic changes in this disease gastroscopically. For these reasons it seems correct, in the light of our present knowledge, to call this disease an inflammation. Atrophic gastritis may develop within a few months, but then it remains stationary. Jones and Benedict were the first to show that in pernicious anemia following liver therapy, the atrophic gastric mucosa may regain its normal appearance. This observation has been corroborated since, and thus we know that atrophic gastritis is not unchangeable.

There is still a third gastroscopic picture of diffuse inflammation of the stomach which we call hypertrophic gastritis. The gastric mucosa looks swollen, velvety, dull, the high-lights are reduced, nodules and *verrucae* are seen. The folds sometimes look segmented, like a caterpillar. Mucosal hemorrhages are often present. If we have the occasion to examine such a mucosa microscopically, we find proliferation of the surface epithelium and of the glandular apparatus, with tremendous infiltration and enlargement of the lymph follicles. The proliferation may become fan-like or finger-like. Not infrequently superficial ulcerations are observed. These superficial inflammatory ulcerations never develop into true chronic gastric ulcer. The site of predilection of the gastritic changes is the body of the stomach, however, antrum gastritis occurs also, although ulcerative antrum gastritis is very rare.

What are the clinical aspects of chronic gastritis? How frequent is this disease? What is its etiology, its symptomatology, its diagnosis, its therapy? What is its relation to other diseases? European workers have called chronic gastritis one of the "central problems" of internal medicine, and from the observation of over 1,500 cases, I am inclined to agree.

In a statistical survey of gastric diseases as observed gastroscopically in 1,000 patients in the United States and in 255 patients in Germany, we found the incidence of chronic gastritis to be 41.8 and 45.0 per cent respectively.<sup>3</sup> For the clinical analysis all cases combined with some other disease had to be discarded. Even so, much care is needed to avoid faulty conclusions. I will try to summarize briefly the results of our analytical efforts.

The etiology of chronic non-specific gastritis is practically unknown. Most is speculation. Very few facts are proved. It seems to be certain that acute gastritis may develop into chronic superficial gastritis and finally into chronic atrophic gastritis. Chronic superficial gastritis is

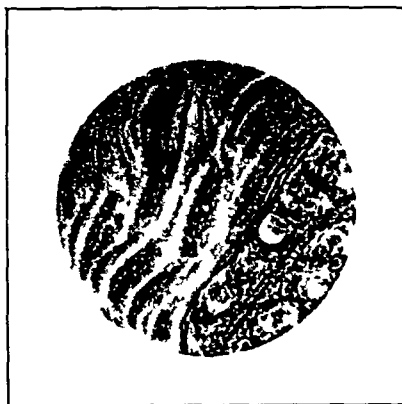


Fig 2 a

Fig 2, a and b

*Gastroscopic (a) and microscopic (b) picture of chronic superficial gastritis*  
 Gastroscopically red patches and layers of purulent secretion are seen  
 Microscopically there is tremendous infiltration with plasma cells only in the upper layers of the mucosa between the crypts and the necks of the gastric glands, one small erosion is seen



Fig 2 b

frequently found together with infection of the sinuses and of the tonsils, or with chronic infectious diseases such as tuberculosis of the lungs. Alcohol does not play any role in my experience. However, it seems that the habitual use of hard liquor may lead to hypertrophic gastritis. All observers agree that nicotine may play an important role. Gastric retention, as found in pyloric obstruction, may lead to chronic gastritis. The continuous reflux of intestinal juice, as found sometimes in stomachs after operation, may produce a very severe form of gastritis. Since this

is a secondary form, it must be omitted from this discussion. Superficial and later atrophic gastritis may be found as a result of high voltage x-ray therapy of the stomach. That atrophic gastritis occurs in various deficiency states, as in pernicious anemia, is well known. With these few statements our positive knowledge of the etiology is almost exhausted. It seems that bacteriological factors play a minor role as compared with mechanical and chemical factors.

When we analyze the symptoms of an anatomical disease, we hope to find complaints so characteristic as to permit immediate diagnosis.<sup>4</sup> Attempts made by all gastroscopists in this direction have been so far without result. Neither case history nor physical examination, nor laboratory, nor Roentgen findings permit the diagnosis, although a few symptoms, especially in atrophic gastritis, are suggestive. In superficial gastritis the patients complain of epigastric pain, either of the delayed type or coming immediately after meals. Indefinite pressure, heavy feeling, fullness, belching, disagreeable taste in the mouth, nausea and vomiting are often present. At the physical examination sometimes, though unfortunately rarely, a sign is found which, in my opinion, is entirely characteristic. However, my description,<sup>5</sup> published in 1926, has never been confirmed. There is sometimes a tender zone to the left of the navel, which when checked fluoroscopically corresponds exactly with the silhouette of the stomach, and therefore cannot be mistaken for left-sided Hæd zones of the pancreas or the left kidney, and certainly not for a tender colon. The roentgenologic statement of a tenderness of the gastric silhouette is the only contribution x-ray can make in this diagnosis. Statement of the thickness of the folds, as seen in the x-ray relief pictures, is not diagnostic. Laboratory findings in superficial gastritis are inconclusive. Histamine proved anacidity may be found as well as hyperacidity. Occult blood may be found sometimes in the stools. Sometimes the aldehyde reaction in the urine is strongly positive, indicating participation of the liver.

If the superficial inflammation leads to atrophy the clinical picture changes. The gastric symptoms become less marked, general symptoms being in the foreground of the clinical picture, so that these patients are always treated as psychoneurotics. Weakness and nervousness come in spells. The reason for this is unknown. Two physicians, both suffering from a severe gastric atrophy, told me that during such an attack, which may last several months, they are incapacitated. When Dr. Murphy of





Fig 3 a

Fig 3, a and b

*Gastrosopic (a) and microscopic (b) picture of chronic atrophic gastritis. Gastrosopically the mucosa is thinned so that the net of the submucosal blood vessels becomes visible. Microscopically the mucosa is thin, the glands have disappeared, the epithelial type has changed, many goblet cells are present.*



Fig 3 b

Buffalo analyzed with me the records of forty-two patients suffering from uncomplicated atrophic gastritis, the question came up whether or not these general symptoms would be found also in other abdominal diseases. A subsequent analysis of a great number of cases of hypertrophic gastritis, ulcer, cholecystopathy, and similar conditions showed that only in pernicious anemia similar symptoms were found, so that the syndrome of epigastric pain, nausea, poor appetite, attacks of weakness and nervousness is highly suggestive of atrophic gastritis, especially if additional

complaints of sore tongue and numbness or tingling in the limbs are present I believe that chronic atrophic gastritis is a very serious disease. It may incapacitate its bearer and, since it may be the precursor of gastric carcinoma, as will be shown later, it must be considered and treated as a major disease. Laboratory findings are of minor importance. Anacidity was found in fourteen out of forty-two cases, two-thirds of the patients did not have anacidity. Occult blood is found sometimes, and in three cases gross gastric hemorrhage was noted, evidently caused by a small inflammatory erosion. Benign obstruction of the pylorus may occur.

Chronic hypertrophic gastritis is also a severe disease. Its symptoms are gastric symptoms highly suggestive of ulcer.<sup>6</sup> Night pain and delayed pain are frequent, but this pain often lasts only a few days, then the patient feels entirely well again, he quickly learns, however, that he must be careful with his diet to avoid a relapse. Gastroscoopically one may see during an attack the gastric mucosa swollen with many scattered shallow gray erosions. A few days later all these erosions are gone but still some hypertrophic areas are seen. Complete cure seems to be rare. Gross hemorrhage as a complication has been observed by all gastroscopists. Fatal outcome is not rare. In some cases x-ray examination gives the picture of the so-called "cob-corn" or granulation relief picture. We found it in Chicago only twice in 300 cases. Flakes of mucus or remnants of food may simulate this picture of dark round holes. We have never succeeded in demonstrating by x-ray the definite localized alterations of the mucosa seen gastroscopically, such as single stiff folds or circumscribed node-formation.

We have seen that, with the exception of a few cases, gastroscopy is the sovereign diagnostic method for chronic gastritis.<sup>7</sup> Difficulties in the gastroscopic diagnosis of chronic gastritis, however, may be experienced also, especially in diffusely infiltrating forms, and the expert may face insurmountable difficulties. These cases, though rare, are important. In a thirty-five year old male the x-ray picture suggested carcinoma of the antrum, the gastroscopic picture was interpreted to be that of an ulcerative antrum gastritis. Through two years the picture remained essentially the same. Granular thickened mucosa with many ulcerations was observed. Finally, rather suddenly, atrophy of the antrum mucosa developed. One month later the patient developed fever and a retroperitoneal tumor. At operation a Hodgkin tumor was found, a biopsy was taken and a biopsy of the antrum was made. The excised stomach wall showed

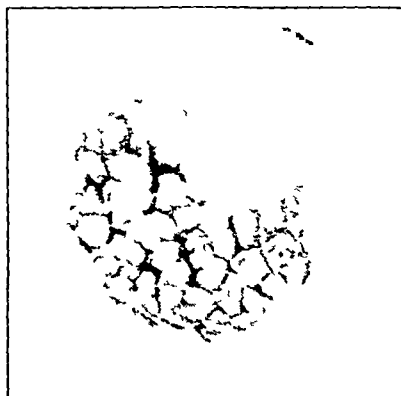


Fig 4a

Fig 4, a and b

*Gastroscopic (a) and microscopic (b) picture of chronic hypertrophic gastritis. Gastroscopically the mucosa is irregular with "cobblestone formation" Microscopically tremendous proliferation with edema and infiltration is seen*



Fig 4b

the typical picture of atrophic gastritis as observed gastroscopically, but not the least sign of Hodgkin lymphogranuloma. In the case of a thirty-seven year old woman with anemia, x-ray suggested polyposis. She had been treated for a severe protein-deficiency state. One year later slight epigastric distress with vomiting developed. The gastroscopic picture was difficult to interpret, all types of diffuse infiltrations were considered. Pyloric obstruction led to immediate surgery, and in this case severe ulcerative antrum gastritis was present. The gross specimen showed

ulcers and inflammatory nodes The microscopic section through the largest ulcer showed that it did not penetrate the muscularis mucosae Cystic atrophic hyperplastic gastritis was seen A section through the nodes revealed the inflammatory character

Recently we observed three cases of tumor causing gastritis I shall describe only one of them A tumor was diagnosed by x-ray, gastroscopically an extensive hypertrophic gastritis had been diagnosed and a bulging in of the lesser curvature had been interpreted correctly as an inflammatory tumor Laparotomy revealed unusual inflammatory changes of the entire interior of the stomach and of almost the entire small intestine as well The folds reached a height of 2 to 3 inches A biopsy was made Microscopically a tremendous proliferation of the mucosa was observed, with edema, hemorrhage and infiltration by plasma cells, leukocytes, and eosinophils The last case of this series of difficult gastroscopic diagnoses shows that the microscopic difficulties may not be less outspoken In a sixty-three year old man, complaining of relatively mild epigastric distress with moderate weight loss, clinical, laboratory and x-ray examination revealed nothing Gastroscopy showed tremendous bleeding, nodular infiltration of the entire posterior wall with many small ulcerations and atrophic areas The diagnosis of a diffuse infiltrative lesion was made and laparotomy was advised The surgeon was unable to feel anything pathological in the stomach, however, he made a biopsy, and microscopically a most unusual section was obtained There was no unity among the pathologists in the interpretation of this section The majority made the diagnosis of lymphoblastoma, but the diagnosis of an unusual form of chronic atrophic gastritis has also been made This unique case must be watched carefully

The therapy of chronic gastritis, as derived from gastroscopic observation, will be discussed very briefly The variations in the picture of such a multicolor disease, of eminently chronic course with many spontaneous remissions, render the judgment of the effect of any type of therapy very difficult In all its forms chronic gastritis should be considered and treated as an important disease Possible etiologic factors, such as infected tonsils, sinusitis, alcoholism, nicotine, should be eliminated A bland diet is always advisable The mechanical work of the inflamed mucosa should be reduced as much as possible Raw cellulose should be eliminated, spices should be avoided in the superficial and hypertrophic forms, but are sometimes recommendable in atrophic forms

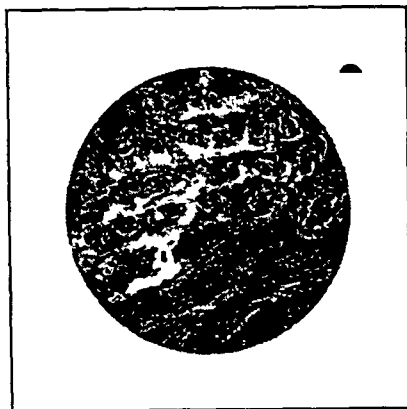


Fig 5 a

Fig 5, a and b

*Gastrosopic (a) and microscopic (b) picture of a rare case of "lymphoblastic gastritis"* These severe changes were found neither by most refined x-ray relief studies, nor palpated at surgical interference, but only at gastrosopic and microscopic examination. Gastrosopically infiltration with erosions and bleeding is seen. Microscopically the mucosa is destroyed by a dense infiltration of lymphocytes.



Fig 5 b

Frequent small meals may be given. If ulcerations are seen, one should insist on rest in bed for a few days with hot applications. Longer rest in bed may be necessary after a gross hemorrhage. In my opinion, gastric lavage is often very useful in superficial gastritis. Lavage is less valuable in the other forms. Alkalis may be agreeable in some cases of hypertrophic gastritis. In atrophic gastritis hydrochloric acid and charcoal sometimes are appreciated. In cases of atrophy in which deficiency states may be suspected, liver may be tried, iron or vitamins, especially nicotinic acid.

Three of our patients with atrophic gastritis responded definitely to liver injections by regeneration of the gastric mucosa. High voltage x-ray therapy was tried first in a case of ulcerative hypertrophic gastritis observed over a period of ten years. The success was amazing, but one year later severe atrophy developed as a late effect of the irradiation. Newer observations confirmed the effectiveness of this type of therapy, however, the end results are still unknown. Surgical treatment, in my opinion, is justified only in the rare cases of gastritic pyloric obstruction. Gastritic gross hemorrhage is a definite contraindication to gastric surgery.

I come to the last chapter, to the complications and sequelae of chronic gastritis. The activity of the bowels is not impaired in uncomplicated gastritis. If diarrhea is noted, inflammation of the intestine may be assumed. The Argentine workers, Royer, Bur, and Montejano,<sup>8</sup> found (gastroscoopically) gastritis in one-third of their colitis cases. In a case diagnosed clinically as Crohn's disease, I found (gastroscoopically) severe hemorrhagic ulcerative gastritis. Chronic cholangitis together with chronic gastritis has been found frequently. In such cases the aldehyde reaction usually is strongly positive. The lesion may be an ascending or a descending one. The latter type with fatal outcome was observed once by myself.

The close relation of gastric atrophy to pernicious anemia is well known. Knud Faber,<sup>9</sup> Hurst<sup>10</sup> and others believed that chronic gastritis is the primary disease destroying the function of the pyloric Brunner glands, a possible source of Castle's<sup>11</sup> antianemic factor. Chester Jones, Benedict and Hampton<sup>2</sup> were the first to observe that liver therapy leads to regeneration of the gastric mucosa. This observation, confirmed by Chevallier and Moutier<sup>12</sup> and Lehmann,<sup>13</sup> speaks, in my opinion, against the correctness of the mentioned theory. Gastroscoptic observations in twenty-three cases of pernicious anemia<sup>14</sup> led to the conclusion that there must be a primary dysfunction of those cells which produce the anti-anemic factor, and a secondary degeneration of the gastric surface epithelium with following genuine inflammation.

Konjetzny,<sup>15</sup> whose extensive surgical and histological work is of the utmost importance, has contended that chronic gastroduodenal ulcer develops from chronic gastritis, and in reality is a gastritic ulceration. This gastritic theory of gastric ulcer is widely accepted in Europe. Konjetzny described a macroscopically visible ulcerative antrum gastritis.

in 50 per cent of all cases of duodenal ulcer he operated upon, and microscopically visible changes in all cases. In American hospitals these changes were not observed, and Walters and Sebening<sup>16</sup> therefore assumed geographical differences. Our gastroscopic observations have failed entirely to confirm Konjetzny's statements. Gastritic ulcerations have not developed into gastric ulcer, and ulcerative antrum gastritis has not been found in cases of ulcer. The relation of gastritis to gastric ulcer as noted in ninety-one cases of gastric ulcer has been studied by Dr Baxmeier of Pittsburgh and myself.<sup>17</sup> Our findings did not support the gastritis theory. In 47 per cent of all ulcer cases, no inflammation was found. We therefore had the idea that differences in surgical technique may be responsible for this discrepancy. Gastric resections and other gastric operations were carried out in twenty-two dogs by Dr H. Necheles, Dr R. Gold and myself<sup>18</sup> with the following results. If a simple resection is made, the resected specimen does not show any pathology. If we filled the dog's stomach with N/10 hydrochloric acid and quickly excised it two hours later, we again found a normal mucosa. But if we filled the stomach with hydrochloric acid of the same concentration and made a resection, a severe ulcerative hemorrhagic antrum gastritis was seen, sometimes proceeding to extensive destruction of the mucosa. If we ligated the arterial blood supply of the left side of the stomach and then cut the stomach out, nothing was seen, but if the operation was performed and hydrochloric acid was used, ulcerative gastritis exactly corresponding with Konjetzny's pictures<sup>15</sup> was found only in the areas without blood supply, sharply demarcated from the other side of the gastric wall. Microscopically we see that the vicinity of the ulcerations is full of plasma cells, an astonishingly rapid inflammatory tissue reaction, which is entirely absent at some distance from the ulcer. These experiments seem to support our gastroscopic observations and to prove that chronic gastritis and gastric ulcer are two different diseases.

Fortunately we are able to support fully Konjetzny's ideas<sup>15</sup> about the origin of gastric carcinoma. Rarely, if ever, carcinoma develops in a normal gastric mucosa. Gastroscopically, as well as microscopically, carcinoma develops in an inflamed mucosa, sometimes in several places, multicentrically. Gastroscopic observation and clinical check prove that frequently atrophic gastritis is a definite forerunner of gastric carcinoma, a precancerous condition.<sup>1</sup> I myself, in 1933, suggested periodical x-ray and gastroscopic examinations of patients suffering from atrophic gastritis.

as the most important weapon in the fight against the most frequent carcinoma. Minimal gastric carcinomas cannot be found otherwise than incidentally, and they will be found incidentally if we decide to carry out periodic x-ray and gastroscopic examinations in patients suffering from atrophic gastritis. The last three case reports will confirm this statement.

A fifty-seven year old patient suffered for more than one year from mild epigastric distress. In the last few months he had some loss of weight. X-ray revealed a prepyloric ulcer. Because of the long case-history, the presence of hydrochloric acid and good response to ulcer therapy, the ulcer was considered to be benign. The gastroscopic picture, however, was that of an extremely small pyloric carcinoma. Atrophic gastritis was found around the lesion. After resection, grossly, no signs of malignancy were discovered, but, microscopically, in full accord with the gastroscopic picture, a minimal carcinoma was found. Its width was 8 mm, the depth 0.5 mm to 2 mm. It is unbelievable that this small carcinoma could have produced symptoms of one year's duration. These symptoms probably were due to the existing atrophic gastritis which also was found microscopically, and probably the discovery of the minimal carcinoma was incidental and due to the careful x-ray and especially due to the gastroscopic examination.

A fifty-four year old surgeon suffered for more than ten years from epigastric distress. Severe purulent cholangitis was found at a cholecystectomy, but the distress was not relieved. The patient developed a histamine proved anacidity, and in the last eight years had terrible attacks of anorexia, weakness and exhaustion. Within the last three years a filling defect of the greater curvature developed. This was thought due to spasm. The defect grew slowly, and when the patient finally submitted himself to the gastroscopic examination, a polypoid tumor was found to lie in an entirely atrophic mucosa. This diagnosis would have been possible two years earlier by gastroscopy. However, the patient recovered after resection. A microscopic section through the edge of the tumor showed the mucosa to be completely atrophic, and the transformation of the atrophic mucosa into tumor tissue was observed. It is a typical case chronic cholangitis, severe chronic atrophic gastritis of ten years duration, slow development of a carcinoma which by periodic gastroscopic examination would have been discovered at least two years earlier.

The last case shows that such incidental diagnoses are possible in



reality A fifty-nine year old man suffered from pernicious anemia and combined cord degeneration Our roentgenologists were unable to find any pathologic change Only for the sake of completeness, gastroscopy was undertaken In the antrum atrophic gastritis was seen, but in the midportion of the stomach toward the greater curvature the ulcerated wall of a small gastric carcinoma appeared X-ray examination repeated with compression and relief films was negative, but at operation a very small adenocarcinoma was excised

Knowledge of chronic gastritis is of outstanding importance in our fight against gastric cancer The following points are the obvious results of these observations 1 Superficial gastritis should be prevented from turning into atrophic gastritis by thorough treatment Therefore it must be diagnosed gastroscopically 2 Atrophic gastritis, the precancerous condition, should be diagnosed This is also possible only gastroscopically 3 If atrophic gastritis has been diagnosed, the patient should be observed, but naturally not told the reason for this observation Every six months x-ray and gastroscopic examination should be undertaken With such a program we may hope to discover carcinomas of minimal size and to bring about cures in a percentage of cases not dreamed of until now, as shown by the presentation of the last three cases Chronic gastritis—a severe disease in itself—derives its most outstanding significance because of its role in the fight against gastric carcinoma

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## MODERN TREATMENT OF SCHIZOPHRENIA\*

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I **I**N DISCUSSING the modern treatment of schizophrenia, I assume that this audience is composed mainly of physicians who are not psychiatrists and who are not experienced in the newer methods of treatment of this disorder. I shall therefore present briefly certain data concerning schizophrenia, its incidence, symptomatology and some of the theories as to its causation together with past methods of treatment. Following this, I shall discuss the newer methods of treatment, their techniques, the theories used to explain their value and the results obtained. Finally, I shall allow myself the luxury, and danger, of certain predictions.

Schizophrenia, or dementia praecox, represents one of the most important medical and social problems facing us at the present time. This disorder usually comes on during late adolescence or early adult life, has comparatively little effect on the life span of the individual, and until recently has shown very little response to any method of treatment. It is the most common type of mental disorder in our state hospitals. Approximately one-fifth of all admissions to state hospitals are cases of schizophrenia, and because it usually results in deterioration but does not shorten life, over one-half of the population of state hospitals is composed of such cases. Since hospitals for mental diseases have slightly more patients than do all other hospitals combined, including general hospitals, children's hospitals, maternity hospitals, and tuberculosis sanatoria, the result is that approximately one bed out of every four of all the hospitals in this country is occupied by a case of schizophrenia. Approximately thirty thousand new cases of schizophrenia are admitted every year to our state hospitals. It seems impossible, therefore, to exaggerate the importance of the study of schizophrenia from the standpoint of its prevalence, its cost to the community, and the amount of suffering which is caused.

Kraepelin gave the term "dementia praecox" to a group of mental disorders variously known as dementia simplex, catatonia, hebephrenia

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and paranoia. He felt that these disorders were to be grouped as a single disease and that all had in common certain qualities, particularly that they came on early in life and led to deterioration. Hence the name "dementia praecox." Bleuler, years later, suggested the term "schizophrenia," feeling that the term "dementia praecox" was a misnomer since, he claimed, all cases do not come on early in life and do not become deteriorated. He regarded the essence of the disorder as a splitting of the psyche, hence the term "schizophrenia." Bleuler likewise includes under schizophrenia a larger group of disorders than Kraepelin did under dementia praecox.

Here, already, we find one reason for difficulty in evaluating any method of treatment. Different clinics disagree in the criteria for diagnosing this disorder. This is particularly true concerning certain acute cases which recover spontaneously. The older Kraepelinians held that no case of dementia praecox completely recovered. If it did, the diagnosis was wrong. Some psychiatrists now insist that a considerable number of cases completely recover and that many more improve greatly with no particular treatment being given.

Almost every conceivable theory has been advanced to explain schizophrenia. Some feel that it arises essentially on an hereditary basis. Others feel that it is explained by some physical factor, such as a brain lesion, an endocrine or metabolic disorder, or an obscure toxemia from foci of infection from other parts of the body. Some feel that it is only to be understood on the basis of psychological factors and that certain repressions and mental conflicts are the actual cause. Finally, there are those who say that it is not a question of either/or, but rather a question of how much of each one of these factors, that is to say, there are a group of psychiatrists who feel that schizophrenia does not arise on the basis of a single cause, but that it is due to a number of causes, some of which may be hereditary, some of which may be organic, and some of which may be psychogenic.

As might be expected, the methods of treatment have depended upon the particular view the psychiatrist had concerning the cause of the disease. If the disease is purely hereditary in nature, it is obvious that the only satisfactory approach is through eugenics and that the disease can be stamped out only by ridding society of a certain stock which is the carrier of the disorder. The organic school has tried all conceivable types of remedies. Particular attention has been paid to the removal of foci of infection and the use of endocrine preparations. While there have been

some very optimistic reports of the results of such treatment, at the present time the general consensus of opinion is that we can produce comparatively little modification of the disorder by such methods of treatment. During the past two or three decades, there has been great emphasis on the psychological treatment, and such attempts have received support partly because other methods of treatment seemed of little or no avail. The use of re-education and occupational therapy has become an important part of the treatment of these cases in all of our best institutions, and has demonstrated that it was of value, although no one has considered it as a panacea. The use of hypnotism, psychoanalysis, and various types of psychotherapy has accomplished, on the whole, comparatively little, although there are those who feel that such methods are extremely valuable and have accomplished more than any other type of therapy that has been used.

While psychotherapy, occupational therapy and the general management and re-education of the patient represent important recent advances in the treatment of schizophrenia and other mental disorders, I shall devote the rest of this paper to certain physiological methods. These can best be grouped under fever therapy, sleep therapy and stimulation therapy.

For many years fever therapy was developed at the Vienna Clinic under Wagner Jauregg. He was able to cure some patients suffering from syphilis of the nervous system and improve many others by inoculating them with malaria. Many other methods of producing fever were developed such as the use of diathermy, hot air cabinets, hot baths, injections of typhoid vaccine, and inoculation with rat-bite fever. These various methods have been tried out extensively in cases of schizophrenia but, in general, the results have been unsatisfactory. The production of aseptic meningitis is another example of the numerous attempts of this sort.

Sleep therapy is commonly regarded as a recent method, yet we find that Dr. John C. Warren of Boston used ether as early as 1847. Later he used *cannabis indica*, known to us now under the name of marihuana. Opium had been used for mental conditions for many centuries. Various authors reported improvement from different types of sleep therapy, but in 1922 Klaesi reported excellent results from prolonged narcosis due to *somnifen*. Other clinics took up the treatment by prolonged narcosis and other drugs such as *hyoscine* and *luminal* were used extensively. *Somnifen* was held by many to be unsafe and its use has been

largely discontinued Sodium amytal, however, has proven itself of definite value and is being used at the present time in a number of clinics throughout the country The effects of this drug are particularly striking in catatonic stupors, certain cases showing remarkable improvement It is difficult to say if this should be regarded as sleep therapy as the immediate result is the disappearance of the stupor so that the patient becomes alert and clear

Various types of stimulating therapy have also been employed and it is of interest to point out that Henry Hurd used monobromate of camphor in 1885 and even produced convulsions in some patients Sodium cyanide, a respiratory stimulant, was first used by Lowenhart in 1918 for cases of stupor He was able to produce temporary improvement in some cases, and a number of patients who had been mute would talk following such treatment Later, carbon dioxide inhalations were used as a form of stimulating therapy Patients would breathe a mixture of carbon dioxide and oxygen, and many stuporous patients could be temporarily brought out of their stupor by this treatment However, little in the way of lasting cures was produced by such treatment, and some psychiatrists felt that the greatest value of carbon dioxide was to enable the psychiatrist to secure contact with the patient during his temporary improved spells, and that by means of the psychotherapy which could then be extended, the real possibility of successful treatment occurred

Gradually, therefore, during the last twenty years, new methods of physiologic treatment have been evolved and gradually the feeling has arisen that we were beginning to develop physiological methods of affecting the schizophrenic process

Recently, the use of two new drugs, insulin and metrazol, has given us still better methods of treatment For a number of years, insulin in small doses has been used for the treatment of various mental disorders, including schizophrenia It was felt that patients showed physical improvement, their appetite improved and they gained weight Some showed mental improvement Occasionally, a patient received an unusually large dose of insulin and went into shock or coma Interestingly enough, several observers reported that patients seemed improved following this large dose of insulin, but none of them followed up this observation or seemed to draw the conclusion that it would be desirable to give large doses of insulin in the treatment of schizophrenia Sakel first made use of insulin as a means of treating morphine addicts He noted

that it had a quieting effect upon them, and felt that this was due to some effect that it produced on the vegetative nervous system Sakel then felt that insulin might be of value in quieting disturbed psychotic patients, and experimented with it Moreover, when noting the improvement that seemed to follow shock or coma produced accidentally, he decided that there was definite value from this treatment and continued to experiment with shock doses of insulin He did not feel that the treatment was specific but rather that the pharmacological shock affected the various vegetative centers and brought about a restoration of normal physiological function Sakel published a number of articles on this subject in 1933-34-35 These articles were combined in book form, and recently this book has been translated into English

As might be expected, Sakel has modified both his theories and his technique of treatment as he has gained more knowledge and experience The essence of the treatment was that patients were given daily sufficient insulin to produce shock or coma After a variable number of treatments, some of these patients either improved or appeared to recover completely Originally, Sakel talked of convulsion therapy and deliberately sought to induce convulsion in some cases However, after a certain amount of experience, it appeared that the patients who went into coma seemed to do better than those who developed convulsions, and for a period of time, emphasis was placed on the value of producing a coma and the dangers from the convulsion were probably exaggerated More recently, and with added experience in treating cases, a more individual type of technique has been developed and the value of one type of shock for certain cases and another type of shock for other cases has been clearly recognized As would be expected, the technique of the treatment has been built up largely by trial and error This is said not in any criticism, since it was the only possible way that our present knowledge could be attained In addition to using insulin, Sakel has again returned to the use of metrazol and has worked out several new techniques for the combined treatment

Sakel originally divided the insulin treatment into four phases In the first phase the patient was given daily injections of insulin, starting with 10 to 30 units and increasing the dose daily until the patient developed shock or coma The insulin was injected intramuscularly early in the morning and the patient would have had nothing to eat since the night before Food was given about four or four and one-half hours after

the insulin injection Phase two began when the dosage was sufficient to produce severe hypoglycemic shocks These shocks might be either coma or convulsions In the development of the hypoglycemic coma the patient would perspire profusely, might have spells of excitement, but would gradually become sleepy and go into coma This would occur, ordinarily, about four hours after the injection of insulin A typical coma of this type was called the wet shock Certain cases, however, would develop during the second or third hour a typical epileptiform convulsion and would not have the profuse perspiration described in the wet shock Sakel referred to this condition as dry shock He also pointed out that there might occur a late epileptiform convulsion during the fourth or fifth hour of hypoglycemia and that this might occur with a typical wet shock Sakel felt that the late epileptiform convulsion was a danger sign and that steps should be taken immediately to terminate the coma A typical dry shock, however, he felt was in some cases desirable and that attempts should be made to induce it, whereas the late convulsion was regarded as undesirable In both cases it was felt that the convulsion was the sign for the termination of treatment Phase two was to be continued from twenty to fifty days Phase three was the term that Sakel applied to a period of rest days which he felt necessary to introduce from time to time At present less emphasis is placed on this phase Phase four was a period of about one week during which the patient was given reduced doses of insulin, and carbohydrates were administered within two hours after the injection Sakel originally felt that it was important to taper off treatment in this fashion, but he now feels that in many cases it is not necessary

The essence of the treatment, aside from the technique mentioned, is the development of the proper type of shock and the termination of the shock at the proper time When it was desirable to produce wet shock, that is, coma, Sakel felt that if necessary drugs such as barbiturates might be utilized to minimize the chance of convulsions developing He also stated that if all external stimuli were kept out and the room was darkened and quiet, the patient was less likely to develop convulsions It was noted that there was a certain critical period in the second and third hours when the patient would most easily develop convulsions If, on the other hand, it was decided to produce convulsions, various measures might be resorted to, such as having the patient in a state of alkalosis, having the patient drink large amounts of water and exposing the patient to external



stimuli during the second and third hours. Furthermore, one might even give such drugs as camphor and metrazol at this time in order that such a convulsion might be produced. The matter of the proper timing of the hypoglycemic state was difficult to decide and could not be settled arbitrarily for an individual case. Early in the development of the treatment Sakel felt that cases of catatonic excitement should be given two or three injections daily, starting with 15 to 20 units, approximately. As soon as the patient responded to insulin by becoming quiet, he was given food. Later, as the procedure developed, treatment was terminated just before the patient went into coma. The treatment for stupor was somewhat similar in principle. In general, sugar was given fairly early. In some cases dry shock was deliberately encouraged. For paranoid cases, Sakel felt that protracted wet comas were the best treatment. However, he stressed the necessity of individualizing and the point that in every case one must determine how the patient reacted to a particular type of treatment and continue accordingly. In general, therefore, one started out with the regular type of treatment, varying it from time to time, and noted how the patient responded to these variations. Accordingly, if the patient responded well to a long, wet coma such treatment would be continued. If he responded satisfactorily to a dry shock, this was continued. Sakel has continued to emphasize this necessity of individualizing the treatment, and all attempts to lay down set rules of treatment have proven unsatisfactory.

The method by which hypoglycemia is terminated depends on the condition of the patient. If able to swallow, the patient may drink sugar water. The general plan is to give a 40 per cent solution of sucrose in warm water. The number of grams of sugar should equal the number of units of insulin plus 10 per cent, so that if the patient received 100 units of insulin, he would be given 110 grams of sugar. If the patient is unable to swallow, the common method of terminating coma is to pass a stomach tube intranasally and thus secure absorption through the gastrointestinal tract. A little atropine may be given to prevent vomiting and spasm. In a case where immediate termination is necessary, glucose solution may be given intravenously. It is important to remember that further sugar should be given in such cases as soon as the patient wakes up, otherwise he is likely to return again to coma.

The maximum period for hypoglycemia should be six to seven hours. Certain dangers may be mentioned. With the abolition of the reflexes,

great care must be taken that the stomach tube is actually in the stomach Sakel discusses a special technique for determining this The second danger is aspiration during coma With the marked increase of salivation and the absence of reflexes, the patient may easily aspirate material into the lungs The patient, therefore, should be placed in a position which will prevent this from occurring A third danger is spasm of different muscles There may be spasm of the vocal cords or of the pylorus of the stomach A fourth danger is that the patient may become chilled due to the excessive perspiration and the decreased heat production This may be guarded against by the use of blankets and of hot water bottles, if necessary Fifth, it should be kept in mind that there are many individual differences in the reaction to insulin, and that on rare occasions patients may get a severe reaction to a small dose of insulin, yet no reaction to a large dose of insulin John reports one case in which an increase of 2 units of insulin in an adult produced a violent reaction, and another case in which a five-year-old child was given 100 units of insulin intravenously twice a day for a whole month with no reaction occurring

I have related very briefly how Sakel came to use insulin shock for the treatment of schizophrenia Space does not permit a discussion of his earlier theories or a detailed critical analysis of his more recent formulations It is obvious that much of the work with insulin was started and carried along on an empirical basis but that, having found a method of value, attempts have been made to explain why it produces these results Sakel has published numerous articles on the subject in which he has attempted to give a theoretical explanation for this method of therapy However, one must admit quite frankly that Sakel's theories as to how insulin benefits schizophrenia are much less impressive and satisfactory than his actual treatment Sakel himself has admitted dissatisfaction with his own theories and has continued from time to time to revise them Quite simply, Sakel's theory might be summed up as follows In schizophrenia new patterns of behavior of an unhealthy nature have been acquired Insulin shock temporarily places the brain at rest and has some effect in obliterating these newly acquired neural pathways When the nervous impulses are blocked from flowing over these newer and abnormal pathways, they revert to the older, normal pathways, this causes normal behavior, or a return to the prepsychotic personality Further discussion of the theoretical considerations of insulin treatment will be given later

The use of metrazol alone as a specific method of therapy for schizophrenia was introduced by Meduna who had been greatly interested in a number of observations by various writers that epilepsy rarely occurred in schizophrenia, and that in some way epilepsy prevented the development of schizophrenia. The following is his own formulation of this hypothesis: "Between epilepsy and schizophrenia there is a biological antagonism. Should it be possible to induce epileptic attacks in schizophrenic patients, such epileptic attacks would change the chemical, humoral, haematological and other aspects of the organism in such a manner that thereby—since the organism so changed would represent an unfavorable basis for the development of schizophrenia—a biological possibility is given for a remission of the disease."

After trying various drugs he used camphor which he felt was of value, but soon switched to metrazol which he felt was much more satisfactory. Briefly, the essence of metrazol treatment is that the patient receives intravenous injection of 5 cc. of 10 per cent solution of metrazol. The exact dosage varies for individual patients and must be determined by experimentation in the case of each patient. The injection is given as rapidly as possible, since if it is given slowly no convulsion is produced. Within a few seconds following the intravenous injection of metrazol, the patient develops a very typical epileptic convulsion. There may be one or two preliminary twitches, sometimes a cry occurs, and the patient then goes into a tonic state which is followed shortly afterwards by a clonic state. The pupils are usually dilated, do not react to light, and Babinski's sign is positive at the end of the clonic phase. Following the attack, the patients are usually confused and often fall asleep, this confusion usually disappears largely at the end of five to ten minutes. The technique of treatment consists in the production of two or three such convulsions a week for a period of three to ten weeks. The length of treatment depends upon the patient's response, some cases clearing up rapidly and other cases failing to show any response whatsoever.

It will be seen, therefore, that Meduna's concept as to the basis for using metrazol is quite different from Sakel's theoretical basis for using insulin. Actually, however, in patients under treatment with insulin, metrazol convulsions are sometimes induced.

Sakel originally used drugs including metrazol to produce a dry shock or convulsion, and others, working in this field, advocated the use of metrazol to produce a convulsion during the second or third hour just

about the time the patient is going into coma. This combined treatment has been used for some time in a number of clinics and is felt to be of value in certain cases, particularly those not responding well to insulin.

Quite recently Sakel has developed a further modification of the combined insulin-metrazol treatment which he regards as of especial value in treating chronic cases and cases which do not respond to other methods of treatment. I quote Sakel's own words in describing this technique: "In cases which have been unaffected by other methods, a protracted or a so-called condensed shock has often proved efficacious. The condensed protracted shock consists of provoking a convulsion in a comatose patient with a small dose of metrazol during the fourth hour of the coma, when he is just on the verge of a late convulsion. The patient then wakes spontaneously and, if desired, may even be left two hours longer in coma. The fact that I have effected improvements just as easily in patients who have only undergone the treatment two or three times, as in those who have been treated over an extended period, points to the conclusion that an amnesia for the psychosis, figuratively speaking, is produced. Physiologically expressed, this means that in such cases we deliberately produce slight injuries to the brain cells, and, by destroying the dominating pathological cells, we assist the dominating healthy cells to break through between those sections which have been producing the psychotic personality."

To understand what common factor there may be in both insulin coma and metrazol convulsions, let us turn for a moment to the study of brain physiology. As is known, the brain metabolizes only carbohydrates, although small amounts of lactic acid and alcohol may also be utilized. In insulin coma the carbohydrates in the blood stream are greatly reduced and studies which we have made at Bellevue show that very little oxygen has been taken out of the blood circulating through the brain. In studying contents of the blood samples of the internal jugular vein and femoral artery, we have shown that there was a fall in the utilization of oxygen of approximately 65 per cent. This indicates that the brain is put at rest by a lack of carbohydrates, although there is an adequate amount of oxygen in the blood. In the metrazol convulsion, the brain is likewise put at rest, but in a different fashion. The oxygen supply to the brain is cut off although the carbohydrate supply in the blood is quite ample.

As a result of studies at Bellevue, the following theoretical considerations have been formulated:

"Insulin hypoglycemia depresses cerebral metabolism by diminishing the food supply of the brain (blood sugar), while metrazol achieves the same effect by decreasing the oxygen available for the combustion of this foodstuff. Thus, insulin therapy affects the brain specially, for that organ utilizes carbohydrates chiefly, while metrazol has a generalized effect on all the organs of the body including the brain. The effect of insulin on the brain is more prolonged, while that of metrazol is more severe. However, in both cases the depression of cerebral metabolism seems to favor the amelioration of schizophrenia."

How valuable are these newer methods of treatment? One can hardly go over the different statistics from the various countries, but in general it may be stated that the large majority of clinics using insulin treatment are convinced of its value, and there is a striking agreement in statistics from these different clinics. The chances of cure depend definitely on the length of time the patient has been sick. Cases of less than six months' duration have much the best recovery rate. This high recovery rate, with some reduction, continues up until about eighteen months, after which there is a marked decrease in the percentage of cures. Many clinics report a recovery rate of from 60 to 70 per cent in cases of less than six months' duration, with improvement in 10 to 15 per cent more. Here, of course, there is room for much argument, first, as to the definite diagnosis of schizophrenia in an early case, and second, as to what constitutes recovery. It can hardly be expected that one is going to make an ideal personality out of a schizophrenic patient who has been treated, and we speak of cures in the same way that we would refer to them with relation to physical disease. In speaking of them, then, we do not assume that the individual has been made over into a perfect specimen physically. Even in most physical disease, when we claim a cure, there are probably some residues, a patient who has had pneumonia may never completely recover so that his lungs are as good as they were before the attack. In fact I believe it is generally assumed that a patient who has had one attack of pneumonia is more likely to have further attacks than is a person who has never had an attack. Yet certainly we speak of such patients as cures, and in the same sense we may use the term cure in discussing the treatment of schizophrenia. A very excellent set of statistics is available from the New York State Hospitals which have now treated over 1,000 cases of schizophrenia by insulin and over 500 cases by means of metrazol. The lumping together of these cases from a number of different hospitals gives us

a good idea of what may be expected by the use of these methods. These figures, while less optimistic than those of some clinics, give clear proof of the value of the two methods of treatment. It also seems to confirm the general impression given by statistics, that the insulin treatment has a slightly higher percentage of recovery to its credit than has metrazol. As to the practical value of these statistics, it would seem that we now have methods of treating schizophrenia which are of great value. However, the possibility of cure is greatly influenced by the duration of the disease. This indicates that we shall probably go through somewhat the same stages in dealing with schizophrenia that we have gone through in treating tuberculosis. There must be a campaign to educate not only the medical profession, but also the general public to the idea that schizophrenia is not a hopeless disorder, and that if diagnosed in the incipient stage, the majority of cases will respond to treatment.

The literature on this subject has become so voluminous that it is impossible to give any complete review of it. It may be pointed out, however, that there are reports from a great many different countries as to the value of the newer method of treatment and that in May, 1937, the Swiss Psychiatric Association held a meeting, the title of which was "The Treatment of Schizophrenia—Insulin Shock, Cardiazol, Sleep Treatment." Dr. M. Mueller, who had previously reported one and a half years before on the use of insulin, discussed the further reports stating "On the whole, however, there is a surprising unanimity as to the actual progress made with the help of the insulin treatment. This is particularly astounding, if we keep in mind that agreements on new methods of treatment have not been very common in our profession. Moreover, in checking the different remission rates, we find that the percentage of discharged patients, whose psychosis was of recent onset, varies between 50 and 80. Compared to this, there are some recent statistics showing that the remission rates for cases of similar duration of illness amount only to 30 per cent." He further states "On the other hand we must not forget how elusive are the clinical features of the genuine schizophrenia. Although such an eminent authority as Bleuler has paid special attention to this problem, we are still inadequately enlightened as to which elements in the picture of schizophrenia should be referred to the fundamental schizophrenic process and which should be regarded as pathologic phenomena or 'superstructure.' In their concept of what is essential in the true schizophrenia, different schools and different coun-

tries are widely divergent I need only remind you of the work of Kleist and the departure of the French and Dutch schools from our Swiss idea of schizophrenia "

Sakel, at this same meeting, states as follows "The therapy dates back to 1928 It is an outgrowth of observations made by me in the course of the attempted treatment of morphine addicts I thought, first of all, that insulin abolished the phenomena of irritation during abstinence from morphine because the nerve cells were blocked and their function quantitatively affected " Sakel relates that he first ascribed the therapeutic effect of hypoglycemia to "cell shock " Sakel then states that he first thought the epileptic seizure was of great value, that he tried strychnine, adjustment in water balance, and the administration of camphor and of metrazol to produce seizures He adds "In the course of years I have, in most cases, abandoned supplementary medication aimed to provoke epileptic attacks With time I have gained the impression that hypoglycemia as such, and nothing else, acts on the psychoses, while the epileptic attack prepares the way by unlocking the gates and altering the psychotic picture " Sakel further discusses his hypothesis, comparing the nerve cell to a combustion engine and the necessity of keeping up the working capacity of the nerve cell by a proper amount of food The idea, therefore, is that insulin produces a diminution of the action of the nerve cell The psychic changes during and after hypoglycemia are explained as follows "I look upon a reaction of the nervous system as a response to stimuli, traversing certain pathways Then the processes in hypoglycemia may be explained by a blocking of pathways previously active so that reactions to the same stimuli run their course over pathways previously inactive Now experience teaches us that the newest and most active organs as well as the most recently acquired pathways are most susceptible to injuries When a nerve cell is injured the pathological change may be qualitative or quantitative "

Two other questions will immediately arise What are the dangers of this method of treatment, and what are chances of relapse occurring When treatment is carried out by well-trained individuals the danger is comparatively slight The mortality rate in our best clinics has been shown to be, I believe, less than 1 per cent At Bellevue where we have been carrying out treatment for nearly two and a half years, we have not yet a single fatality Obviously, if persons past middle age are subjected to this treatment, there is considerably more risk than there would be in

younger persons. Cases of high blood pressure or cardiac disease are also poor risks, and can only be treated if this fact is clearly understood. The United States Veterans' Bureau, where most of the psychiatric patients are now over forty years of age, reports fairly encouraging results following the use of these two methods of treatment, results, which considering all the adverse circumstances, are sufficiently optimistic to make those who have treated such cases eager to continue doing so.

Fractures and dislocations occur at times as a result of the convulsive seizures. A recent report of compression fractures of the bodies of the lower dorsal vertebrae deserves further study. It is stated that most of these fractures are asymptomatic and will only be discovered by careful X-ray studies. Attempts are being made to prevent such fractures by putting the patient in extreme flexion or using some type of body cast or brace. It should be emphasized, therefore, that the use of insulin or metrazol is not a simple procedure to be carried out indiscriminately by untrained persons. Rather it should be regarded as one does a surgical operation. It is not without danger but the possibility of curing or improving patients who would otherwise never recover, justifies the risks taken.

Concerning the question of permanence of cure, it is still too early to make any positive statements. We know that a certain number of cases do relapse, but many times such cases respond favorably to a second course of treatment. In studying our own cases that relapsed following insulin treatment, we have been struck by the fact that many of them were cases who had comparatively little treatment. In the beginning we were, naturally, very conservative, probably too much so, and the result was that in these earlier cases when the person seemed to be responding well we terminated treatment and returned the patient to the community much sooner than we would now do. I feel, therefore, that a number of relapses are due to improper or inadequate treatment and that as time goes on our technique will have improved so that we will have fewer such relapses. A second point, which to me is of great interest, is that a number of cases that we have discharged as only slightly improved have continued to improve after return to the community so that some of them, after six months or a year, are now put down as cures. This is a very hopeful sign and a result which we had not anticipated in the beginning, and is worth calling to your attention. The fact that there is still a chance for improvement or even cure in a patient who has re-



sponded only slightly to thorough treatment should make us all take a more hopeful attitude in returning these cases to the community. As to what will happen to patients many years after treatment, we cannot, of course, say at this time. However, even if a patient who was regarded as a cure were to relapse after a number of years, it might still be said that the treatment had been worth while and of definite value.

What should be most emphasized is that the use of insulin and metrazol has given us a weapon which enables us to attack and treat successfully in a relatively high percentage of cases, a disease which up to now has responded very little to any method of treatment. A study of the effect of this treatment should help us to get some idea concerning the nature of this unknown disorder which we label schizophrenia or dementia praecox. Personally, I doubt if either insulin or metrazol will remain with us long as the best method of treatment. I believe that we shall soon gain such a knowledge of this disorder that we will perfect still better methods of treatment. In this connection it is of interest that, while working with us at Bellevue on the study of the physiological changes produced by insulin and metrazol, Himwich was convinced that a simpler and better method of treatment could be formulated. If the deprivation of energy to the brain resulting from both insulin and metrazol treatment was the cause of the improvement, he felt that a simpler method of producing the same result might be worked out. As a result, an attempt was made to produce a similar type of response by having a patient breathe pure nitrogen, using an ordinary anesthesia mask with soda lime for removing carbon dioxide, the patient was allowed to go into a state of acute anoxia until he became unconscious and developed slight convulsive twitchings. Pure oxygen was then switched on and the patient quickly regained consciousness. Interestingly enough, the patient had no sense of suffocation and claimed that the treatment was not unpleasant, he also stated that he felt somewhat better as a result of the treatment. A personal communication from Himwich informs me that he has now treated four cases by this method and all four show a full remission. In this therapy the patient is subjected to three such treatments a week, thus resembling metrazol in the number of treatments given and also in the acute anoxia produced.

It would seem, therefore, from what I have presented this afternoon, that we have developed two methods of great value for treating one of the most common types of mental disorder which heretofore responded

but little to any type of therapy. Indications are that we will continue to improve our methods of therapy, that we will gain a further understanding of the nature of this disorder and that we may even achieve a method of prevention. At the present moment, I emphasize the point that we should not regard these conditions as hopeless and that the general practitioner has a definite responsibility with regard to the early diagnosis of such disorders and for seeing that treatment is instituted at the earliest possible moment, since it is clearly established that every day of delay in the starting of treatment definitely decreases the patient's chance of recovery.

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## DEATHS OF FELLOWS

MEYER, MONROE ABRAHAM 57 West 57 Street, New York City, born in New York City, August 1, 1892, died in New York City February 27, 1939, graduated in medicine from Cornell University Medical College in 1916, elected a Fellow of the Academy November 6, 1930

Dr Meyer was a Fellow of the American Medical Association and a member of the American Psychoanalytic Association, the American Psychiatric Association, the American Psychopathological Association, and the County and State Medical Societies

PARRY, ANGENETTE Huntington, Long Island, New York, born in Rome, New York, October 5, 1857, died in Boston, Massachusetts, March 1, 1939, graduated in medicine from the Woman's Medical College of the New York Infirmary for Women and Children in 1891, elected a Fellow of the Academy December 6, 1894

Dr Parry served as a member of the Executive Board of the American Women's Hospitals since its inception in 1917 She was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Medical Women's Association and one of its former presidents, a member of the Women's Medical Society of New York State and one of its former presidents, and a member of the State and County Medical Societies

Dr Parry spent four years as one of its volunteers at the Kokkinia Refugee Hospital at Kokkinia, Greece For her work there she received a decoration from the Government of Greece

VOISLAWSKY, ANTONIE PHINEAS 33 East 68 Street, New York City, born in New York City, June 5, 1872, died in New York City, February 22, 1939, received the degree of Bachelor of Science from New York University in 1894, graduated in medicine from Dartmouth Medical College in 1897, elected a Fellow of the Academy May 7, 1903, designated a Fellow in Otolaryngology in 1933

At the time of his death, Dr Voislavsky was chief of clinic and attending rhinologist and otolaryngologist to the St Luke's Hospital, consulting otologist, rhinologist and laryngologist to the Harlem Eye and Ear Hospital, the Staten Island Hospital and the Northern Westchester Hospital, and consulting rhinologist and laryngologist to the Ruptured and Crippled Hospital and the Flower-Fifth Avenue Hospital

Dr Voislavsky, who was awarded a certificate from the American Board of Otolaryngology, was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the American Laryngological Association, the American Laryngological, Rhinological and Otolological Society, the American Otolological Society and the County and State Medical Societies He was a director of the Alumni Federation of New York University, and was at one time president of the Society of Alumni of St Luke's Hospital During the World War, Dr Voislavsky served on the Medical Advisory Board of the Secret Service

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BULLETIN OF  
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JUNE 1939

GENIC AND HORMONAL FACTORS IN  
BIOLOGICAL PROCESSES

*Harvey Lecture, April 20, 1939*

C H DANFORTH

**D**URING the last forty years biologists in increasingly large numbers have been turning their attention to genetics, and during the last thirty years other biologists, also in increasing numbers, have been concentrating on the endocrines, so that at the present time one or the other of these phases of the subject is of prime interest to a large proportion of students of biology and scientific medicine. But the methods and frequently the materials, employed by the two groups are so different that the number of investigators who have interested themselves and are well-informed in both fields remains relatively small.

It is not surprising that seeming inconsistencies have arisen, but it is a part of our scientific faith that real inconsistencies do not exist and argument over heredity vs. environment or genes vs. hormones is useful only insofar as it tends to clarify the nature of factors or processes which are interdependent and mutually indispensable. With the diversity of approach as great as it is, it becomes incumbent upon us to attempt from time to time to clarify and evaluate not merely our own findings but those that have been obtained by different means and by other investigators.



in order that we may have a clearer and more harmonious view of the whole

Since the time of Darwin it has been customary to look at biological problems phylogenetically, with the result that in his reflective moments the biologist feels a little uncomfortable if he cannot postulate some way in which the structures or reactions in which he is interested might perhaps have been evolved. This phase of the subject rarely permits of exact analysis, and reflections upon it are likely to be in a measure unsatisfactory and pre-eminently tentative. Nevertheless the craving for a working hypothesis constantly besets us and may perhaps, with due caution, be indulged at times. To this end it may be expedient to consider, insofar as limitations will permit, a few general implications of recent findings and in the light of these attempt to interpret some of our data relating to secondary sex characteristics.

It is obvious that no one can adequately summarize or properly relate material in fields so vast as endocrinology and genetics. These subjects do not stand out by themselves as two sharply defined domains of science, but have contacts with and transitions into such other fields as those of nutrition, biochemistry and experimental embryology. For the present purpose let us glance first at the genes, hormones and organizers, then consider some evidence bearing on the evolution of sex, and finally attempt to synthesize a point of view with reference to a particular problem, the significance and regulation of sex differences. It may be stated at once that the sequence of presentation is by no means the sequence in which the data and conclusions were developed.

### THE GENES

What is frequently referred to as "Mendel's First Law" is still the corner-stone of genetics. Indeed, the basic phenomenon of genetics is believed to be the independence and discreteness of the individual gene. Reproducing itself precisely, except for rare mutations, the gene is in effect "immortal" in the Weismannian sense. Though it may be associated in succeeding generations with various alleles, it is not contaminated by them and always emerges from each new combination as pure as an atom released by the breakdown of a chemical compound. While most geneticists doubt if any gene has actually been rendered visible, and some think the nature of the gene is such that it never can be seen, an immense amount of evidence on the position and function of various

*loci* in the chromosomes has been accumulated and there is fair agreement on fundamental concepts of segregation, linkage and other now familiar genetic phenomena which were scarcely dreamt of in the earlier years of genetic study (Darlington<sup>1</sup>, Dobzhansky<sup>2</sup>)

One especially important respect in which genetic concepts have undergone a distinct evolution relates to the effect of the genes on somatic traits. It is no longer customary to think of genes as forming a kind of microcosm which mirrors in a way the adult organism (as did the germs envisioned by some of the preformationists). On the contrary, the tendency now is to think of the whole complex as functioning together, but with some genes more important than others in effecting the production of any individual trait. The late Doctor Calvin Bridges illustrated this point graphically by drawing an analogy to a weighing balance, so set that it would tip when all of a certain number of weights of various sizes had been added to one of the pans. The scale would respond only when the last weight, no matter which it might be, was added, and yet the last weight need be intrinsically of no more importance than any of the others. One cannot speak of *the* gene for a particular trait except in the sense that the gene in question is the differentiator in the production of that trait. Under other conditions the seemingly significant gene for the same trait might be an entirely different one.

How the genes exert their influence is still problematical. They are surrounded and maintained by the cytoplasm, which they in turn affect, apparently in two ways. They determine, or at least influence, the reactivity of cytoplasm to both internal and external stimuli and at the same time themselves furnish part of those stimuli. Occasionally cytoplasm may early acquire properties which persist throughout life (Boycott *et al*<sup>3</sup>, Goldschmidt<sup>4</sup>), and possibly for even more than a generation. There is a suggestion, coming from hybridization followed by repeated back crosses, and from polyploids in plants (von Wettstein<sup>5</sup>) that normal morphology is at times conditioned by a certain concordance between genes and cytoplasm. In this, one might perhaps detect a hint that reactivity to genes, even to a particular gene, may have been a matter of gradual cytoplasmic adjustment or evolution, but as yet evidence from such animals as *Drosophila* and pheasants gives little obvious support to this idea. Even so, it is doubtful if all cytoplasm is equally responsive to all genes. Indeed one might conceive embryological differentiation to be due to a progressive acquisition by the cytoplasm of a capacity for

reacting with genes to which it had previously been unresponsive. Presumably the same genes are present in all of the cells at all of the stages in the history of each individual, but some of these genes become effective only when the cytoplasm has passed through certain preliminary phases. Perhaps even at the cellular level there is some kind of analogy between the processes of ontogeny and phylogeny.

Whatever the evolutionary sequences may have been, it would seem proper to regard the relations we now find between cytoplasm and genes as a kind of functional symbiosis. The actual anatomical and physiological reactions are essentially cytoplasmic but, as has been abundantly shown, the behavior of the cytoplasm is conditioned by the genes which are associated with it at the moment or have recently been so associated. That this adjustment has come about through evolutionary processes going on within the cell now seems probable.

### THE HORMONES

The early concept of a hormone as a substance produced by the cells of one part of the body and effective on those of another part is still acceptable. But to refer to hormones as chemical messengers is perhaps a little more figurative than our present concepts should permit. The hormones are usually thought of, justly no doubt, as activators or stimulators, but it is important to remember that they produce their final effects only through such protoplasm as will respond to them. They do not stimulate inanimate matter and, as will be pointed out presently, a hormone may have a very different effect on the same tissue of related species, or even individuals, and on different tissues of the same species or individual. The specificity of most of the hormone-tissue reactions is apparently more properly an attribute of the tissue than of the hormone. It seems to be largely a question of whether or not the tissue will utilize the hormone if it is available. With reference to the prevailing concepts this is perhaps stating the case backwards, but it may contribute something to clarity if we occasionally look at the matter from the less familiar angle.

From this point of view each hormone appears as just another component of the total environment to which all of the cells are subjected. That the hormones may in some measure permanently influence or condition the cytoplasm in a manner analogous to that in which the genes do, is suggested by embryological and experimental findings (Steward<sup>6</sup>). But on the whole their effects seem to be, if sometimes scarcely

less profound, at least generally more transient than those of the genes. That one hormone or another is absolutely essential to the normal realization of many biological functions<sup>7</sup> is abundantly indicated by an immense amount of published evidence too familiar to call for comment. It is also known that chemically similar substances, and also some synthetic products which may not be actually identical with true hormones at all, can be made to serve adequately in their place. To an evolutionist this presents a challenging problem. What is the significance of the hormones phylogenetically? In attempting to answer this question it is doubtful if one should limit himself to the hormones alone.

Until rather recently we have been inclined to think of the hormones as more or less peculiar to vertebrates, and especially distinctive of mammals. Moreover, we have been possibly a little too much disposed to draw sharp lines of demarcation between hormones and vitamins, and between both of them and simple chemical and physical factors on the one hand and genic influences on the other. Of late the barriers seem to be breaking down. Even in insects, hormones are now receiving much attention (Beadle and Ephrussi<sup>8</sup>, Kuhn<sup>9</sup>, Wigglesworth<sup>10</sup>). It appears that in certain species of insects a single hormone effective on some of the tissues is produced by several different organs, each with its own primary function. In other species, where its function, if any, is unknown, this same hormone may still be produced in significant amounts. One might suspect that the appearance of a hormone may ante-date phylogenetically any adaptation of the tissues for its use.

#### ORGANIZERS AND VITAMINS

The popular tendency that would attribute directive or creative powers to hormones has been carried to an extreme with reference to organizers. The very word suggests active determination, but it would seem that here again there is a disposition to mistake the passive means for the active agent. Organizers, like hormones, seem to be only components, albeit essential ones, in the environment of normally developing cells. Ordinarily they do not "organize" or "determine" in any strict sense but to speak figuratively, function as "go signals" for cells which otherwise might wait. Apparently, as cells of an embryonic system reach a certain stage of development they may give off substances which when added to the milieu of cells of another system enable the latter to differentiate according to their own intrinsic potentialities. In the absence of the

appropriate organizer the cells may remain undifferentiated or even follow some other course (as in potential lens tissue, Lewis<sup>11</sup>, Stockard<sup>6</sup>) This is of great importance in embryogenesis and also throws light on a possible path of protoplasmic evolution

From some points of view the vitamins have much in common with the hormones and organizers The chief difference seems to be that the vitamins are synthesized outside the animal body, but it is not certain that this distinction is a very valid one

### INTER-RELATION OF FACTORS

It is not the purpose here to do more than suggest that at least some of the vitamins are merely substances upon which protoplasm has become dependent through evolutionary adaptation, and that the hormones may be either rather complex vitamins which the body has evolved the capacity to synthesize, or metabolic components of the internal environment to which there have been evolutionary responses analogous to those elicited by factors in the external environment That the whole problem of food, vitamins and endocrines can be reduced to really simple terms is quite unlikely, but there is good reason to think that there has been an interesting evolution of specialization with reference to hormones and vitamins as well as to other external factors To cite but one example, some evidence might indicate that the estrogens which play such an important role in the mammalian reproductive cycle are phylogenetically older than the mammals themselves Indeed it may be that they were first evolved by the plants, and the reason they are estrogens at all is inherent in the cyclic or seasonal character of plant growth How much evolution there has been in the hormones since animals began to elaborate them for themselves is an interesting problem whose solution lies mostly in the future Riddle<sup>12</sup> has made some very interesting contributions to this phase of the subject in his studies of prolactin

When we attempt to evaluate all these diverse factors, we are led in each case to the cytoplasm as the reacting system The cytoplasm is obviously adjusted to respond to influences which emanate from the genes within and the hormones, vitamins and similar factors from without

### THE PROBABLE EVOLUTION OF SEX

One of the primary functions of sex is apparent to the geneticist who makes use of it in the improvement of domestic plants and animals Sex

affords above all else a means for combining in one individual favorable traits from a variety of sources. If it were not for amphimixis, each desirable trait would be in conflict with every other good trait except in the rare cases where several favorable mutations chanced to occur in the same germ line. In the absence of sex, if favorable genes were to appear in different lines, they would only serve to increase the competition between those lines, with the probable extermination of some and the consequent loss of desirable genes. But under a system of sexual reproduction, germ lines which enjoy advantages due to favorable heredity are likely to be brought into contact with each other when, instead of being purely competitive, their good qualities may be combined by interbreeding and preserved and multiplied by natural selection. Sexuality, therefore, may be presumed to have had the effect of changing favorable mutations in different germ lines from necessary antagonists to potential synergists. Without sexual reproduction it is doubtful if the kind of protoplasm which early appeared in our world could ever have reached a differentiation much beyond that of the simpler plants and animals. There are, of course, other important aspects of sexuality, but the advantages alluded to would alone seem to offer sufficient reason for its evolution, once the function of conjugation had appeared.

Of the many kinds of sex that may have arisen among the Protista, it seems likely that the kind which gave rise to sex in the higher plants and animals, must at first have involved only the gametes. Botanists long ago pointed out what looks like a plausible sequence leading from zoospore to isogamous gametes, to heterogamous gametes and finally to the egg and sperm of oogamy (Allen<sup>13</sup>). The concomitant evolution of the soma seems to have been from plants or animals in which (a) any cell at all might break up into vegetative reproductive units or gametes, either isogamous or differing in sign, through (b) those in which only certain cells function in reproduction with the gradual evolution of special organs in which such cells can develop, to (c) the final segregation of two classes of individuals each of which suppresses the production of one or the other type of germ cells and so can function only as a male or a female. Briefly, it appears that sex started as a difference between germ cells and has evolved into a difference between individuals.

If we turn now to consider the conditions under which the morphological aspects of sex develop, a number of interesting features emerge

In the first place, study of lower forms shows us that the kind of dimorphism exemplified by sex is not a unique phenomenon. It represents a rather common tendency toward what, to borrow a word from the bacteriologists, we might call pleomorphism. It is probably not essentially different from the dimorphism or polymorphism that results when individuals of some plant or animal species, if subjected to different environmental conditions, assume correspondingly diverse forms. Environmental factors in such cases are not necessarily directive in any sense other than that they act as "trigger mechanisms" to set off one or another train of possible reactions. When such responses fall in a continuous series, they excite no special interest, but when they are discontinuous, and especially when there is some suggestion of the "all-or-none", curiosity is aroused. That a plant is large when grown in rich soil and small when grown in poor soil is not particularly exciting, but if it has one kind of leaves in water and another on land, we are impressed.

Structural adaptation for the production of male or female germ cells seems to be merely one of these alternative responses, which may be conditioned by a variety of external factors. It is found to be so in an immense number of existing species where the genic constitution is such as to permit the reproductive tissues to develop indifferently into either an egg-producing or a sperm-producing organ. But in many species each new individual receives a set of genes with a differential bias in favor of one sex or the other. This is accomplished through the elaboration of the familiar XX-XY complexes. But such a differential as is established by an XX or an XY serves merely as one influence among the many to which the developing cytoplasm is adjusted to respond. There is little evidence that cytoplasm containing one of these chromosomal complexes is any more responsive to that particular complex than it would be to the alternative one. The sex-chromosome influence may be, and often is, outweighed by other internal or external factors. It is difficult to say whether in its evolutionary development the chromosomal control of sex has been perfected through an intensification or multiplication of the factors whose balance is determined by the XX and XY combinations, or by an increase in the sensitivity of protoplasm to those factors which already existed. A few illustrations will serve to emphasize how great are variations in the adequacy of the chromosomal regulation of sex differentiation.

## CHROMOSOMAL DIFFERENTIATION

The differences between species strongly suggest an evolutionary sequence. In a vast array of lower animals each individual may produce either sperm or eggs, and we have learned something of the conditions which regulate these two types of activity. Two especially effective differentials are age and season. When sex is associated with season it may be mediated through some hormonal or prehormonal substance of the sort considered in the next section. But in all these cases where sex is conditioned by external factors it is clear that the potentialities of both sexes are inherent in each individual. Chromosomal determination is brought about through the intensification of differentials which were already present but so well balanced that the scale could be tipped only by some external factor.

The mollusks are particularly interesting in this connection. Many of them seem to be without a chromosomal bias in favor of either sex. For example, in some of the pteropods sperm and eggs may be seen developing almost simultaneously in the same gonad (Danforth<sup>14</sup>). Among bivalves the oyster, as Professor Coe<sup>15</sup> has pointed out, presents an interesting series of conditions indicating a range from no sex bias at all to a feeble tendency toward internal control, but almost always with a marked disposition to protandry. But of all the mollusks thus far described the gastropod, *Ariolimax californicus*, is among the most interesting. In genetic and ecological studies of this species, C. C. Wright\* has shown that chromosomally there are two sexes, XY males and XX females. The XY individuals apparently invariably function as male throughout life. The XX individuals, however, are protandrous, behaving as typical males during the early part of their life after which they lose their external copulatory organs and from then on behave as true females. In this species the chromosomal differential is obviously not quite strong enough in young individuals to overcome a widespread molluscan tendency to protandry, but it becomes wholly effective when the animal reaches full maturity.

Among the Amphibians, especially the Salientia, the chromosomal sex mechanism can be over-ridden fairly easily as many investigators have shown (e.g. Witschi<sup>16</sup>, Burns<sup>17</sup>), and even among higher vertebrates we find evidence that chromosomal determination is not necessarily final. But there would be little ground for any suspicion that a



chromosomal mechanism is intrinsically inadequate for sex control. Indeed, there is no reason to suppose that any extreme to which sexual dimorphism has thus far led could not have been regulated entirely by the chromosomes, as it still seems to be in some of the insects, with no need of any hormonal differentials whatever.

### HORMONAL DIFFERENTIATION

Purely intracellular regulation of function is not well adapted for coordination. To this defect we are probably largely indebted for development of the nervous and endocrine systems. In respect to the latter, some of the lower plants are rich in hints of possible evolutionary sequences. It has been known for a long time that among the algae there are certain, mostly periodic, environmental conditions that help to regulate the reproductive cycle. Various authors have gathered evidence that light in changing intensity, temperature, and especially substances dissolved in water may at times stimulate conjugation or gamete formation. But not all related species react in the same way to the same stimuli (Danforth<sup>18</sup>). That the factors on which a species depends for its stimulation should characteristically become effective at the very season which is best suited for the propagation of that particular species is probably not a mere coincidence. It may conceivably have come about by some chance fitness or preadaptation of the protoplasm to its environment. But it seems much more probable that favorable reactions were gradually evolved through protoplasmic alterations and natural selection, to the end that there have developed many kinds of protoplasm each adapted to respond to some particular set of environmental conditions. Perhaps adaptations at this really biochemical level may in fact constitute one of the most significant aspects of evolution, and one which may yet lend itself to precise analysis.

The recent studies of Moewus<sup>19</sup> on reproduction in *Chlamydomonas eugametos* seem to mark a step in this direction. He finds that in the proper media vegetatively reproducing plants without cilia can be propagated in the dark. Brought into the light such plants soon develop cilia and motile gametes. But even when left in the dark the cells may be made motile and reproductive by the addition of filtrates from cultures grown in the light. When such filtrates are added, one class of gametes, which may be called "female", is activated first, followed a little later by activation of the other class. The substance which is effective on

these cells is produced in an inactive form by cultures growing in red or orange light. When the filtrate from such cultures is subjected to blue or violet light it passes rather rapidly through a series of phases. First, after a few minutes of exposure, it acquires a capacity to activate "female" gametes, then it becomes inactive for a short time, followed by a brief period in which it activates "male" gametes, after which it remains completely and permanently inactive toward all gametes. Moewus<sup>19</sup> further reports that identical results may be obtained if, instead of the filtrate, a carotinoid, crocin, is added to *Chlamydomonas* cultures grown in the dark. Finally by mixing two crocin derivatives, each by itself inactive, either the female-stimulating or the male-stimulating substance can be obtained, depending on the proportions in which the two ingredients are combined.

Such manifestations are rather suggestive of the hormonal activity we see in higher forms. In *Chlamydomonas* they seem to approach a degree of chemical simplicity that permits one to hope they may ultimately become understandable. It is easy to imagine that in its evolutionary history *Chlamydomonas* protoplasm acquired the capacity to elaborate several crocin esters and then to react with them in such a way that gametes should be produced and activated at a time and in a manner that is advantageous for continuity of the species. How the chemical make-up of the protoplasm has become adjusted to give these reactions is by no means obvious. It is still more baffling that at reduction-division the contents of a single cell can so segregate as to give two cells, one of which will be activated by one mixture of chemicals, the other by a different mixture of the same chemicals. These are fascinating problems for those who can cope with them, and their solution is bound to do much to clarify our ideas of evolution. But in the meantime there is no justification for relinquishing the morphological approach or a point of view which permits us to look upon the development of function as "purposeful," in a biological sense.

Among the lower animals a number of species have been studied in which sex seems to be determined by environmental factors of a chemical nature. In the classic case of the worm *Bonellia* (Baltzer<sup>20</sup>), it seems that whenever an undifferentiated larva comes in contact with a female it becomes attached to her proboscis and develops as a small parasitic male. In the absence of an opportunity to indulge this particular tendency it becomes a female except that a larva isolated *in vitro* may be made to

become a male or an intersex by adding much or little of an extract of female tissues, or even certain salts. We may suppose that instead of any mysterious potency in extracts of female *Bonelliae*, what is really demonstrated is an evolutionarily acquired adaptive capacity on the part of the larva to react in a characteristic way to certain conditions, if it meets them, and in another way, if it does not.

It would not be profitable in this connection to attempt to review all the evidence of hormonal regulation of sexual development and function in the lower forms<sup>21</sup>, but it may be recalled in passing that if we are not too restrictive in our definitions, such regulation may be said to be of widespread occurrence. With some birds, such as the brown Leghorn fowl, certain characters seem to be almost completely under hormonal control. In laboratories where special experiments are being carried on with this breed, even a professional poultryman would find it exceedingly difficult, if not impossible, to determine the original sex of some of the birds on the basis of comb and plumage alone. Genetically male and genetically female Leghorns which have had their original gonads removed and then been subjected to the same kind of implants or injections come to be similar almost to the point of identity in some of their more conspicuous characteristics.

For the mammals there is an appreciable body of literature, familiar to this audience, indicating that among some of them too there may also be a considerable degree of equivalence in the capacity of male and female somatic tissues to respond to either male or female hormones<sup>22-23</sup>. One need mention in this connection only such striking examples as the freemartin in cattle, "sex-reversals" in the guinea pig, changes resulting from parabiosis, and the intersexes of both genotypes which have recently been produced in mice and rats by injecting pregnant females with excessive amounts of male or female hormones (Hamilton and Gardner<sup>24</sup>, Green and Ivy<sup>25</sup>). Moreover, the extraordinary interrelation of the mammalian pituitary and other glands concerned with reproduction, for a knowledge of which we are greatly indebted to the pioneer work of the president of this society, makes mammalian endocrinology a subject to tax the research capacity of the most gifted.

We can not yet infer how general or, in the case of some species such as man himself, just how complete hormonal determination may be (Dantchakoff<sup>26</sup>, Raynaud<sup>27</sup>). But it is safe to say that there are mammals in which at least some traits may be fully conditioned by hormones,

and this almost irrespective of the initial chromosomal constitution

And so we may conclude from this survey not only that it is entirely within the range of biological possibility for a high degree of sexual specialization and dimorphism to be determined by either a genic or an endocrine background, but that both types of determination are in fact realized<sup>28</sup> For our present discussion it is immaterial whether the extra-cellular or "humoral" differentials are established by experimental means or result from the hereditary idiosyncrasies of some endocrine gland (Smith and MacDowell<sup>29</sup>) In either case it seems simplest to look upon the reaction as a matter of protoplasmic adjustment where the emphasis should be placed not on the stimuli but on the protoplasm which integrates and utilizes them The prospect of an early and adequate analysis would be brighter if it were not for the fact that both modes of response have developed side by side in the same lines This situation is clearly revealed by the types of plumage dimorphism in birds, which I would now like to discuss briefly as illustrative material

#### GENES AND ENDOCRINES IN RELATION TO THE PLUMAGE OF BIRDS

In studies on birds the conventional procedures involving removal of glands, with or without replacement therapy, injection of hormones, hybridization and skin transplantation have on the whole yielded harmonious results when applied to any one species or race, and often seemingly discordant results when applied to different species\* It may be worth while to review some of these results briefly, citing a few specific experiments

There are certain characteristics which distinguish the feathers of each part of the body, but many transplantations of skin<sup>31</sup> from one part to another have resulted in no change in the character of the feathers produced In some species a change of hormonal level will, and in others, will not affect the plumage, irrespective of whether or not transplantations have been done Among a few of these strains genetically determined changes in the threshold of responsiveness to hormones are known to have occurred, and in all of them there are regional differences in responsiveness which have been acquired embryologically Taken together they afford interesting parallelisms between "phylogenetically" and ontogenetically acquired differences Transplantation of skin from one sex to the other yields especially illuminating results and shows what

\* Dominko<sup>30</sup> provides an excellent discussion and bibliography covering this field

wide interspecific differences really exist

A piece of skin transplanted at hatching from a male to a female dwarf turtle dove has for several years produced feathers indistinguishable in size and color from those of a male, and quite different from surrounding feathers from the female's own skin. Since the volume of the original transplant was less than that of one of the many feathers which it has since produced we may infer that there is no longer anything of significance in the graft except the genes and cytoplasm descended from those originally transplanted. It would seem that in this case the female produces no hormones whose actions differ, so far as the feathers are concerned, in any respect from those of the male. Injection and castration experiments in doves, pigeons, guinea fowl and a number of other species indicate that such lack of differential effects of male and female hormones on plumage characters is not an uncommon one. In this group, as in others, the very same hormones may or may not, according to the species, affect other secondary sex characters such as bill color or development of gonoducts.

When a transplant similar to that in the dove was made from a male to a female common pheasant<sup>32</sup>, the feathers produced by the transplanted skin were different from those of either a male or a female, showing a kind of compromise both in color and in structure. With grafts made in the reciprocal direction, again a compromise was obtained, but one different from the first. In these pheasants we find four very distinct types of plumage corresponding to the four possible combinations of male and female hormone, male and female protoplasm and genes. This is true of several kinds of pheasants and, judging from the findings of Stadie<sup>33</sup>, is probably also true of a number of the European songbirds.

When instead of the preceding species, brown Leghorn chicks were used for both donors and hosts, the feathers produced by each graft were like those of the host irrespective of the sex of the donor. In other words, the Leghorn is at the opposite extreme from the dove. In the dove sex differences in plumage are regulated by genes without reference to hormones, in the Leghorn they are regulated by hormones without reference to genes. If in adult Leghorns there are any traces of the genic effects seen in pheasants, they are at the very best only slight.

But there are other races of fowl in which the reactions are different. Various experiments in skin transplantation between Campines and Leg-

TABLE

## GENIC AND HORMONAL FACTORS IN THE PRODUCTION OF PLUMAGE DIMORPHISM

Chromosomes	Sex hormones	Types of plumage in four different genotypes			
		A	B	C	D
WZ	F	1	1	1	1
ZZ	F	4	2	1	1
WZ	M	1	3	1+	4
ZZ	M	4	4	2	4
WZ	O	1	3+	4—	4
ZZ	O	4	4	4	4
WZ	F+M	1	1	1	1
ZZ	F+M	4	2	1	1

WZ, female, and ZZ, male sex, F, ovarian, M, testicular, and O, none 1, dove, guinea fowl and others, B, common pheasants such as Reeves, ring-neck and others, C, fowls of the Campine-Sebright group, D, fowls of the Phoenix breed and, approximately, the Leghorn-Plymouth Rock group 1, female plumage, 4, male plumage, 2 and 3, intermediate plumage

horns,<sup>34</sup> as well as exchange of gonad transplants and hormonal injections have shown that the Campine fowl has feather follicles whose threshold for hormonal stimuli are very different from those of the Leghorn. A Campine follicle can produce the same kind of feather as the corresponding Leghorn follicle, but it does so only under the influence of a quite different hormonal balance. From genetic evidence it appears that a single gene difference is responsible for the divergent reactions in these two races. The young of both these and other birds produce a series of juvenile feathers which seem to indicate a progressive adaptation to the hormonal or genic factors with which they will ultimately react more fully.

The table summarizes what might be characterized as four types of adult reaction between genes and hormones, or, better, four ways in which different forms of protoplasm respond to these internal and external factors. It is quite possible, indeed probable, that the arrangement in the table does not correspond to any particular evolutionary sequence, but it does show the kind of diversity which would seem to provide for evolution of special types of response. When it is recalled that the differences in reaction shown in columns C and D are due to but a single gene, it is not surprising that one finds diversity of response to be due

much more often to difference in tissues than to difference in hormones. As an example of this diversity it may be mentioned that all of the four types listed give their own individually characteristic responses to comparable doses of the same mammalian estrogen.

In addition to the experiments just mentioned, it has been found by chance that a much more delicate type of transplant is possible. This is because of the tendency of young pigmentoblast cells to wander, occasionally crossing the line between graft and host. This results in production of mosaic feathers which are found in most series of transplants and have been studied recently with great success by Willier and his colleagues<sup>35</sup>. In some of these mosaics where a few pigmentoblasts of one type may become relatively isolated in a foreign environment, the responses, or lack of them, are as characteristic as when there has been no operation at all. Again it seems to be the cells and not the hormones that determine the reactions.

Finally, when the humoral complex, which thus far has been considered as a unit, is analyzed with respect to its components, a still greater diversity is revealed. To cite only a single example, Professor Witschi<sup>36</sup> and later Doctor Stadie<sup>33</sup> found that, whereas in many species the pituitary stimulates the gonad and that in turn influences the feathers, there are some species (e.g. in the genus *Pyromelanus*) in which the follicles have acquired the ability to react directly with the gonadotropic hormone itself. This is precisely what might be expected to have happened on the basis of the general thesis that tissue-hormone reactions are in large measure determined by protoplasmic adaptations to already existing substances which happen to be present at the time when it is biologically desirable that the reaction take place.

### SUMMARY

Experimental study of factors controlling sex differences in the plumage of birds has led to the conclusion that it is necessary to regard the hormones as essentially non-specific substances to which tissues of different species may or may not develop a capacity to respond. The situation found to exist in birds, and in other species of animals and plants as well, leads to the suggestion that one aspect of evolution may have involved a progressive adjustment of the cytoplasm to both intracellular and extracellular factors. It appears that the genes give character to the cytoplasm or "condition" it, while at the same time supplying substances

with which during development it becomes progressively adapted to react. Adaptations to hormones and organizers seem to be of much the same nature as those to genic effects. Apparently each new adjustment has come about primarily through a chromosomal alteration which imparted to the cytoplasm the capacity to utilize some substance already at hand.

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## CLINICAL AND PATHOLOGICAL ASPECTS OF ACUTE LEUKEMIA\*

CLAUDE E. FORKNER

**A**CU TE LEUKEMIA is not a very rare disease. Its clinical diagnosis may be exceedingly difficult. Frequently acute leukemia must be considered in the differentiation of obscure disorders. It is the purpose of this address to review some of the important points with regard to the clinical, hematological, and histological characteristics of the disease.

Dr Paul<sup>14</sup> has told you that the test for heterophile antibodies does not invariably distinguish infectious mononucleosis from acute leukemia. I think we can go still further and say that no procedure is available which will tell with certainty early in the course of illness whether a patient is suffering from acute leukemia or a leukemoid state. A number of disorders, some of them benign, may closely simulate and indeed at times be indistinguishable from acute leukemia. It must be within the experience of many of you to have seen patients in whom you have diagnosed acute leukemia and later, owing to the favorable outcome of the disease or to the acquisition of new data, have been gratified to witness your diagnostic error. The medical literature contains scores of references to such cases, often regarded as remissions or cures of the disease, but probably more correctly interpreted as leukemoid states or as secondary or symptomatic leukemia. This subject will receive further consideration later in my address.

### THE CLINICAL PICTURE OF ACUTE LEUKEMIA

The disease may occur at any age, in any race, and in either sex. Authentic cases of leukemia in newborn infants have been recorded. It is of interest that all of the leukemic newborn infants and young children have had non-leukemic parents, whereas infants born of leukemic parents, of which there are about fifty well-documented cases in the literature, have in no instance been afflicted with the disease.

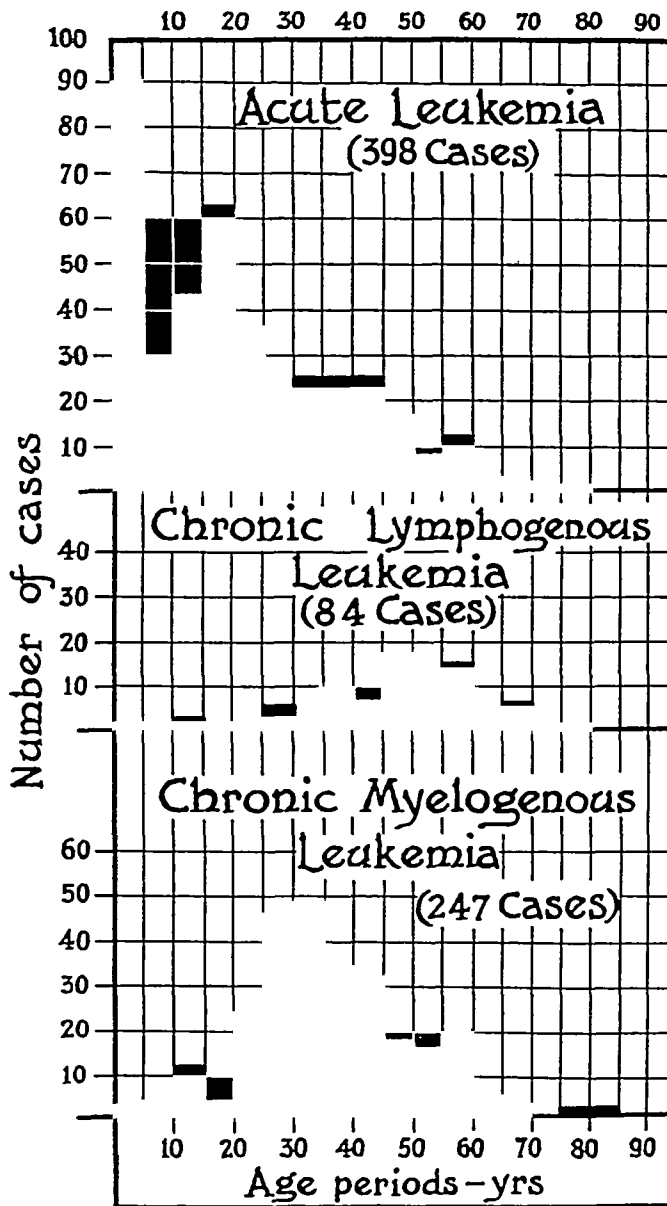


Fig 1—The age incidence of three varieties of leukemia, arranged in periods of five years (Modified from the data of Ward<sup>1</sup>)

Figure 1 illustrates the age incidence of acute leukemia in relation to the age incidence of chronic forms of the disease. It is apparent that the acute disease has a tendency to occur at an earlier age than chronic leukemia. The graph is modified from that of Ward<sup>1</sup>. You will note that although rare, acute leukemia may occur at an advanced age. I

TABLE I

PROPORTION OF SEXES AT VARIOUS AGE PERIODS  
IN 929 CASES (WARD<sup>1</sup>)

<i>All ages to age of</i>	<i>Acute leukemia</i>		<i>Chronic lymphemia</i>		<i>Chronic myelema</i>	
	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>
5	60	40	—	—	—	—
10	65	35	—	—	—	—
15	69	31	75	25	60	40
20	72	28	80	20	61	39
25	71	29	83	17	55	45
30	71	29	61	19	52	48
35	70	30	76	24	52	48
40	69	31	86	14	52	48
45	68	32	75	25	53	47
50	68	32	77	23	55	45
55	67	33	75	25	54	46
60	67	33	77	23	56	44
65	—	—	73	27	56	44
70	—	—	74	26	56	44
75	—	—	74	26	56	44
80	—	—	75	25	56	44
85	—	—	—	—	56	44

have myself observed a typical case supported by postmortem study in a man eighty years of age. Additional evidence was presented by Warren.<sup>2</sup>

Leukemia in all of its forms is more common in the male, but the course of the disease in the two sexes appears to differ in no important respects. Table I, taken from the data of Ward,<sup>1</sup> shows the sex incidence of acute and chronic leukemia at various ages. It will be noted that the preference for the male is not so marked in the earliest age group as in subsequent groups. These observations were confirmed in the studies of Minot and his associates.<sup>3</sup>

The onset of acute leukemia may be insidious or abrupt. In about 50 per cent of patients, the beginning of illness is like that of a respiratory infection, often with fever, sore throat, cough, and general malaise. The patient is thought to have catarrhal fever, grippe, influenza, or tonsillitis, but instead of prompt recovery, prostration persists, the patient continues to feel badly, to have fever, he develops pallor and a tendency to bleed from the mucous membranes and into the skin. Sometimes the

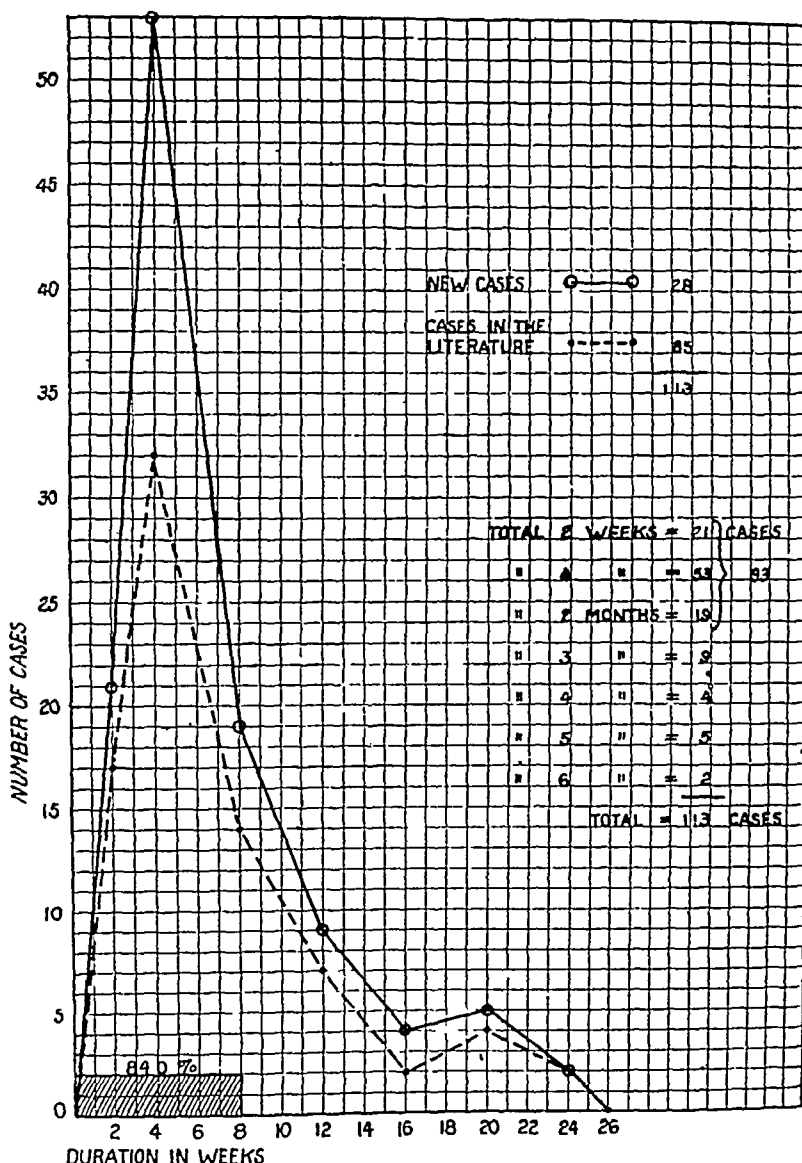


Fig 2—Duration of illness on 113 patients with acute leukemia (Warren)

onset, particularly in children with acute lymphocytic leukemia, simulates closely that of acute rheumatic fever, as has been stressed by Cooke,<sup>4</sup> Smith,<sup>5</sup> Sutton and Bosworth,<sup>6</sup> and others. Baldridge and Awe<sup>7</sup> found acute arthritis in thirteen of twenty patients under twenty-one years of age suffering from lymphocytic leukemia.

The onset of acute leukemia may be marked by bleeding from the gums or aching of the teeth so that the patient believes the origin of his trouble is a local disorder in the mouth. Such patients, before they are

seen by physicians, frequently consult dentists who may perform extractions or other operative procedures which are followed by uncontrollable hemorrhage, osteomyelitis of the jaw, or extension of an ulcerative process

Among other symptoms which may appear early in the disease and which cause patients to seek medical advice are fever, tachycardia, enlargement of lymph nodes, weakness, disturbances of vision, and irregularities of menstruation. Early in the course of the disease no significant anemia may be present, but occasionally pallor, the result of anemia, may be the first manifestation which brings the patient to his physician.

As a rule, the steady progressive course of acute leukemia is unchecked either by natural agencies or as the result of treatment. A number of isolated instances of spontaneous remission and a few cases of apparent cure have been recorded. Warren<sup>2</sup> recorded the duration of the disease in 113 cases (Figure 2), ninety-three per cent of the patients died within two months and all within six months. The causes of death are varied. There may be terminal bronchopneumonia, septicemia, or hemorrhage. Agranulocytosis may precede death or occur at any phase of the disease. Severe prostration, myocardial failure, or progressive anemia may be precipitating causes of death.

Before proceeding with a discussion of the differentiation of the various types of acute leukemia, I wish to provide you with a simple classification of the leukemias (Table II) in order that you may be better oriented concerning the remarks to follow. Time does not permit that we consider this aspect of leukemia in detail, but the subject has been presented elsewhere by Forkner.<sup>8,9</sup> Leukemia, in general, is classified on the basis of whether it is acute or chronic, leukemic or subleukemic (aleukemic). Many workers prefer to indicate the site of origin of the cells which are concerned and to designate the types as myelogenous (myeloid or medullary) or lymphogenous (lymphoid or lymphatic). Other workers prefer to designate more specifically the strain of cells primarily involved. For example, one may speak of acute or chronic lymphocytic, monocytic, or eosinophilocytic leukemia. The fourth column in Table II gives a list of the specific types of acute or chronic leukemia which may be encountered. The more common types are indicated in capital letters. It is these types that I wish to discuss particularly.

TABLE II  
CLASSIFICATION OF LEUKEMIA (LEUCEMIA, LEUKOSIS, LEUCOCYTIEMIA)

CLINICAL DESIGNATION	GENERAL TYPE OF LEUKEMIA	CELL OF ORIGIN	SPECIFIC TYPE OF LEUKEMIA (Common types indicated in capital letters)	SYNONYMS DEPENDING ON COMMON USAGE, ON COURSE OF THE DISEASE OR ON CLINICAL OR HISTOLOGIC CHARACTERISTICS
LEUKEMIA OR SUBLEUKEMIC (ALEUKEMIC) LEUKEMIA (Acute or chronic)	Myelogenous (Arising from cells of bone-marrow)	Myeloblast	Myelophylic LEUKEMIA	Myelogenous, Myeloid, Myelocytic or Myeloblastic Leukemia Myelosis
			Eosinophilic Leukemia	Eosinophilic Leukemia
			Basophilic Leukemia	Basophilic Leukemia
			Chloroleukemia	Chloroma or Chloroleukosarcoma
			Erythroleukemia	Leukemia Associated with Erythremia
	Lymphogenous (Arising from cells of lymphoid tissue)	Megakaryoblast	Megakaryocytic Leukemia	
		Lymphoblast	Lymphocytic LEUKEMIA	Lymphogenous, Lymphoid, Lymphatic or Lymphoblastic Leukemia, Lymphoblastoma Leukemicum, Lymphadenosis
			Leukosarcoma	Lymphosarcoma Associated with Leukemia
	Lymphogenous or Myelogenous	Primitive Mesenchymic Cell	Stem Cell Leukemia	Hemohistioblastic, Embryonal or Lymphohistiocytic Leukemia
		Plasma Cell Myeloblast Lymphoblast	Plasma Cell Leukemia	Plasmacytoma with Leukemia or Multiple Myeloma with Leukemia
Disputed		Monoblast	Monocytic LEUKEMIA	Histiocytic Leukemia, Reticulosis, Reticuloendotheliosis, Reticulum Cell Leukemia, Reticulosarcoma

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THE DIFFERENTIATION OF THE VARIOUS TYPES  
OF ACUTE LEUKEMIA

Since acute leukemia is a fatal disease and cannot be treated satisfactorily by any known therapeutic agent, there exists the feeling among some physicians that attempts to subclassify the disease into various types of acute leukemia are not justifiable. This attitude, although it is the path of least resistance, does not advance knowledge of the disease, leads to the inadequate study of cases and hence confusion in the medical literature. Many of the textbooks of medicine and of the papers on leukemia state that all types of acute leukemia are identical in their symptoms, although it must be admitted that all patients with acute leukemia do not exhibit the same symptoms.

Another reason that acute leukemias often are not separated into their various subtypes is that to do so is difficult and has required exceedingly careful study of the blood cells by expert hematologists using all available methods. In the following remarks I shall stress certain important clinical signs which have been too little appreciated and which aid greatly in complementing and substantiating hematologic differentiation of types.

About four decades ago, Gilbert and Emile-Weil<sup>10</sup> distinguished three principal types of acute leukemia according to the prevalence of the main symptoms. Their first type was the rare but typical acute leukemia with enlargement of the lymphoid tissues as the predominant feature. Their second type was the hemorrhagic form characterized by an intense hemorrhagic diathesis. The third type described by these workers was the buccopharyngeal or the anginous and pseudoscorbutic form with hemorrhagic infiltrations and necrotic, ulcerative processes in the oropharyngeal cavity. These were purely clinical types and were not known at the time to be correlated with any hematologic criteria.

Working independently and without a knowledge of the earlier studies of Gilbert and Emile-Weil, I had the opportunity a few years ago, while working at the Thorndike Laboratory in Boston, to study intensively a considerable number of cases of acute myelogenous, acute lymphogenous, and acute monocytic leukemia. We were able by hematologic methods, confirmed by the study of pathologic specimens, to separate these three main types of acute leukemia. When these hematologic types were correlated with the clinical pictures it became apparent



that the buccopharyngeal or pseudoscorbutic type of Gilbert and Emile-Weil was, hematologically, acute monocytic leukemia, that their hemorrhagic form was, hematologically, acute myelogenous leukemia, and their type with enlargement of lymphoid tissues, was acute lymphocytic leukemia. On the basis of further studies we were able to formulate, even more completely, definite syndromes associated with the different types.

#### LESIONS OF MUCOUS MEMBRANES AS AN AID IN DIFFERENTIATING ACUTE LEUKEMIAS

It was our opinion in 1934,<sup>11</sup> and this has been supported by subsequent observations, that diffuse marked swelling of the mucous membranes, particularly of the gingivae, usually with ulceration and necrosis, was characteristic of acute monocytic leukemia and usually was absent in acute leukemia of the lymphocytic or neutrophilocytic (myeloblastic) types. Frequently diffuse cellulitis with swelling and pain, together with signs of acute inflammation extending into the deeper tissues of the face, was present. Because of these presenting symptoms, patients often consulted their dentists prior to being seen by physicians. Patients with acute lymphogenous and acute myelogenous leukemia frequently have symptoms referable to the mouth and other mucous membranes, but in my experience these lesions usually are of a different sort and are limited to hemorrhages and slight infection.

#### THE SIZE OF THE SPLEEN AND LYMPH NODES IN ACUTE LEUKEMIA

The spleen in acute myelogenous leukemia often is enlarged somewhat but usually it is not palpable, whereas in acute lymphogenous leukemia the spleen almost without exception is felt two or more centimeters below the costal margin. In acute monocytic leukemia the spleen is palpable in the majority of cases and may be conspicuously enlarged. In four of my cases the spleen at autopsy weighed from 360 to 1065 grams.

Almost invariably there is distinct general enlargement of the lymph nodes in acute lymphogenous leukemia. In acute monocytic leukemia the lymph nodes, particularly those in the neck, may be slightly or moderately enlarged, but general enlargement to the extent found in acute lymphogenous leukemia is not present. It is even more uncommon to find generalized enlargement of lymph nodes in acute myelogenous

leukemia and, if any enlargement is found, it is slight in degree

Because of these characteristic lesions of the mucous membranes, and of the spleen and the lymph nodes, which were closely correlated with hematologic and autopsy findings, it has become possible to make a satisfactory clinical differentiation of the acute leukemias even when the blood picture is not clear cut or when other tissues do not become available for histologic studies

### HEMATOLOGIC DIFFERENTIATION OF THE ACUTE LEUKEMIAS

There are five important characteristics of the blood in acute leukemia (1) The dominant leukocytes (usually over 80 per cent) are of uniform and immature type There are exceptions to this general rule in certain cases of acute lymphocytic, acute monocytic, acute eosinophilocytic leukemia and chloroleukemia In these latter disorders the cells may appear more mature and the leukocytes resemble those of the chronic rather than the acute disease When a very large proportion of the leukocytes are myeloblasts, lymphoblasts, and monoblasts, there may be almost no intermediate stages in development This renders difficult deductions as to the type cell by observation of intermediate phases in maturation This difficulty is further accentuated by the fact that, owing to the greatly disorganized hematopoietic system, immature cells of other strains than that of the type cells may be present in moderate number in the blood (2) A second characteristic of the blood in acute leukemia is that the total number of leukocytes may be subnormal, normal, or increased Frequently the total number fluctuates widely Leukopenia of a severe grade may be present at any phase of the disease and commonly is present in both acute myelogenous and acute lymphogenous leukemia near the time of onset of the disorder (3) Blood platelets are markedly decreased, sometimes absent Too little attention is directed in general medical clinics to observations of blood platelets and their variations Study of these structural elements is of great importance in the differentiation of acute leukemia from many other diseases They may contribute the most significant clue in a difficult diagnosis Warning should be given, however, against accepting the results of routine direct enumeration of the platelets except when this is done by an expert and checked by examination of a good blood smear (4) The coagulation and bleeding times usually are prolonged (5) Anemia develops rapidly, although at the beginning of the disease no significant anemia

may be present. Except when complicated by chronic loss of blood, the anemia is of the normocytic and normochromic type. Frequently, immature erythrocytes are present and the number of reticulocytes is increased.

The number of blast cells is frequently so large and the intermediate phases in maturation of the type cells are so few that it may be exceedingly difficult to determine whether the blast cells are myeloblasts, monoblasts, or lymphoblasts. Under these conditions some workers have classified the leukemia as being of the stem cell or embryonal cell type. On the other hand, careful study, at least in my experience, of cases regarded by others as stem cell leukemia, usually has demonstrated that the type cells belong to one of the three main strains, namely, myeloblasts, monoblasts, or lymphoblasts.

The "supravital" technique is of particular value in the differentiation of the monocytic strain of cells and aids materially in the recognition of early myelocytes and their immediate precursors, the myeloblasts. There are, moreover, certain finer distinctions in cell types which are present in ordinary Wright's stained smears. The nuclei of myeloblasts are large, round, oval or slightly indented and contain several nucleoli. The cytoplasm is deeply basophilic and uniform in character. The nuclei of monocytes, premonocytes, and monoblasts, for the most part, tend to have complicated shapes and possess very few nucleoli. The cytoplasm is relatively abundant, is generally not very basophilic, and contains many dust-like granules.

Another useful means in the differentiation of the various types of acute leukemia is the oxidase or peroxidase reaction. The shade of color and the size of the positive granules in monocytes are somewhat different from those in the myelocytes and myeloblasts. The size of these granules in monocytes usually is smaller and their number fewer than in myelocytes or so-called myeloblasts.

#### HISTOLOGIC DIFFERENTIATION OF THE ACUTE LEUKEMIAS

Patients with acute leukemia in whom the hematologist has difficulty, likewise present distinct problems for the pathologist. It happens rather frequently that pathologists are in a less favorable position to make a precise diagnosis of the type of leukemia than are the internists. One of the chief criteria upon which the pathologist relies is the oxidase reaction of the tissues. If the cells infiltrating the liver, kidney, and other tissues

are oxidase positive and if the architecture of the blood-forming organs is disorganized and shows indiscriminate hyperplasia of uniformly immature leukocytes, the diagnosis of myelogenous leukemia is made. On the other hand, if such a state exists, but without a positive oxidase reaction, the diagnosis of lymphogenous leukemia or of lymphoblastoma is in order. With the discovery of a third type of leukemia, monocytic, the pathologic diagnosis became more difficult, because in this type the oxidase reaction of the blood and tissue cells may be either positive or negative and hence the chief point for the differential diagnosis is lost.

There are, however, certain characteristics of the histology which are of great importance, which are little appreciated, and which usually are distinctive. Although it is often extremely difficult or impossible in good paraffin sections to distinguish lymphoblasts from myeloblasts, this is not true of monocytes and their precursors. The monocytes, when observed by means of the oil immersion lens in the blood, or in their sites of formation in the tissues, have certain characteristics distinguishing them from myeloblasts or lymphoblasts. The nuclei, even of premonocytes and of monoblasts, usually are of irregular shape, often in the form of irregular crescents or of broad elongated bands bent on themselves. Frequently, the nucleus may be bent on itself several times giving the impression of lobulation. There exist also many young monocytes, the nuclei of which may be of simpler structure, but they exist as close companions of the cells with the more complicated nuclei. The nuclei of the monocytic series of cells rarely have demonstrable nucleoli, whereas these structures are common in lymphoblasts and are even more prevalent in myeloblasts. The cytoplasm of premonocytes and monoblasts as a rule is more abundant and much less basophilic than that of either lymphoblasts or myeloblasts.

A point of importance is the degree of infiltration and obliteration of the normal architecture of lymph nodes. It is well known that in lymphogenous leukemia the lymph nodes generally are overgrown by diffuse proliferation of lymphoid cells destroying the essential organization of the nodes. In myelogenous leukemia many lymph nodes may be involved with myelogenous leukemic infiltrations, but usually there is preservation of the architecture of the node. Now in acute monocytic leukemia the involvement of the lymph nodes histologically is conspicuous and of an intensity closely approximating that of lymphogenous leukemia. The essential architecture may be completely destroyed

TABLE III

DIFFERENTIATION OF THE THREE MAIN TYPES OF ACUTE LEUKEMIA  
(FROM FORKNER<sup>9</sup>)

	Acute Myelogenous Leukemia	Acute Lymphogenous Leukemia	Acute Monocytic Leukemia
Spleen	Usually not palpable	Almost invariably significantly enlarged	Palpable in about 70 per cent of cases
Lymph nodes	Usually slight or no enlargement	General enlargement of moderate or marked degree	Moderate in neck but other lymph nodes very slightly en- larged, if at all
Liver	Usually palpable	Usually palpable from 1 to 4 cm below costal margin	Usually palpable from 1 to 4 cm below cos- tal margin
Mucous membranes, particularly of mouth and pharynx	Petechiae, bleeding often slight swelling of gingivae but rarely ulceration	Petechiae, bleeding, rarely ulceration	Petechiae, bleeding, usually marked, dif- fuse swelling of gingivae or pharynx with ulceration, often cellulitis with swelling and tenderness of face, marked fetor oris
Histologic distinctions of type cells in blood and tissues	Oxidase reaction	From few to many oxidase positive cells, with from few to many coarse granules	All lymphoid cells oxidase negative
	Other charac- teristics	Dominant cells myelo- cytes "A" (Sabin) and myeloblasts nuclei round or oval usually with several nucleoli, cytoplasm deeply basophilic, myelocytes "B" (Sabin) present, Auer's bodies fre- quently present in few cells	Dominant cells lym- phoblasts and young lymphocytes, nuclei round, oval or slightly indented with few nucleoli usually pres- ent, relatively small amount of deeply basophilic, hyaline cytoplasm, mature lymphocytes present in fair number, occa- sional myelocytes "C" (Sabin) and meta- myelocytes present
			Dominant cells mono- blasts and premono- cytes, nuclei usually elongated and folded deeply indented or otherwise irregular in contour, nucleoli rarely present cyto- plasm relatively abundant usually not deeply basophilic and not hyaline but slightly basophilic and "ground glass like" Auer's bodies may be present in few cells, mature monocytes present in significant and vary- ing numbers, myelo- cytes "C" and meta- myelocytes often present in small numbers

It is thus apparent from the preceding discussion that acute leukemia can be differentiated clinically, hematologically, and histologically into various types. By means of the accompanying Table III, I wish briefly to recapitulate the essential points in the differentiation of the three types of acute leukemia.

### LEUKEMOID STATES

There is one further point that demands consideration in any discussion of the acute leukemias. What are the diseases with which they may be confused, and how does one separate a so-called leukemoid state from a true leukemia? Infections of various sorts may produce clinical and hematologic pictures resembling closely or remotely those of acute leukemia. This has been so striking that some workers, for example Wallbach,<sup>13</sup> believe that a sharp borderline between infection and leukemia does not exist. In connection with this it should be stated that the possibility of leukemia of man being a virus disease is still open. The fact that considerable evidence suggests that leukemia is a neoplastic process has not settled the question and has done little to advance our knowledge with regard to its etiology.

Perhaps the disease with which acute leukemia is most easily confused is infectious mononucleosis. You have noted in the paper by Dr. Paul<sup>14</sup> a detailed presentation of the characteristics of this disease. In addition to the heterophile antibody test, there are other points which often distinguish the two disorders. Chief among these is the behavior of the blood platelets. Whereas in infectious mononucleosis the platelets are, as a rule, little if any affected, in acute leukemia, almost without exception, the platelets are greatly decreased. Associated with this, the tendency for spontaneous purpura or other hemorrhage is present in acute leukemia but usually absent in infectious mononucleosis. Often the degree of immaturity of the leukocytes is greater in acute leukemia than in infectious mononucleosis. The oxidase or peroxidase reaction, when positive in the immature cells, indicates that they are not lymphogenous in origin and so this test is of value in excluding infectious mononucleosis. In acute leukemia nucleated red blood cells are often found in the smear whereas this does not occur in uncomplicated infectious mononucleosis. Anemia develops rapidly in acute leukemia whereas in infectious mononucleosis this factor is not conspicuous. Biopsy of an enlarged lymph node may be useful in differential diagnosis but often this is not essential.

Acute disseminated miliary tuberculosis sometimes is associated with striking abnormalities in the blood picture with an outpouring of many immature leukocytes. In a number of instances the true diagnosis has been revealed only at autopsy. Roth,<sup>15</sup> Marshall,<sup>16</sup> Wiechmann,<sup>17</sup> Thompson,<sup>18</sup> and others have reported such cases.

Whooping cough, especially when complicated by bronchopneumonia may be associated with leukocyte counts of from 50,000 to 300,000 per c mm of which a high percentage (up to 90 per cent) may be lymphocytes. Acute leukemia, especially in children, may be accompanied by intractable cough associated with mediastinal masses. The differentiation of the two diseases may at times offer difficulties until close attention is given to the details of the blood picture.

Acute agranulocytic angina frequently is confused with acute leukemia. Indeed, acute agranulocytosis may occur as a complication in an otherwise frank case of either chronic or acute leukemia. In agranulocytic angina, 90 or even 100 per cent of the leukocytes present may be mononuclear forms. Many monocytes and a few myelocytes may be present at the beginning of the recovery phase. Unless one is cautious in interpreting such changes, they may be mistaken for manifestations of leukemia. Here again careful study of the details of the blood picture as well as a careful history, especially with regard to the taking of drugs, will lead to the correct interpretation.

Neoplasms, especially when the liver, spleen, lymph nodes, or bone marrow are involved by miliary metastases, may give rise to leukemoid blood pictures. Leukocytosis up to 140,000 per c mm and with the presence of many myelocytes, myeloblasts, and nucleated red corpuscles has been observed. The picture more often simulates that of chronic than acute leukemia.

Osteosclerosis, Hodgkin's disease, multiple myeloma, poisoning with chemicals, and infection with pyogenic organisms may at times be confused with acute or chronic leukemia.

### TREATMENT

Little has been said concerning this phase of the subject. No form of therapy provides any permanent relief. Transfusions of blood are of fleeting value. It is important, however, not to lose hope when one is treating such patients. Every effort must be expended in attempting to find some other explanation than leukemia for the altered state of the

patient Although we cannot cure the disease, it is my belief that progress is being made and that sooner or later someone will discover the secrets which until now have remained hidden

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## CHRONIC GASTRITIS CLINICAL ASPECTS\*

BURRILL B CROHN

CHRONIC gastritis should be defined as a protracted inflammatory lesion involving one or more coats of the stomach wall, with a characteristic histological picture and gross pathological changes, with a typical or at least generally distinctive symptomatology and a known clinical course and progression. These criteria, while not necessarily constant, should be more or less uniform to deserve the appellation of a clinical entity.

The diagnosis of chronic gastritis was current perhaps a century ago, little understood and vaguely recognized. Its popularity was replaced by a functional or secretory phase of interpretation which was ushered in by Kussmaul with the introduction of the flexible stomach tube, and carried on by Ewald and Boas (1885) and more latterly by Rehfuss and his school of followers (1914). In more recent years the nervous (Leube) or functional or psychic explanation of gastric disorders replaced in public opinion all other causative and etiological explanations of symptoms relative to the epigastrium and, whether of cerebral or psychic or autonomic nervous system imbalance (Eppinger and Hess), achieved first place in clinical recognition.

With the application of the x-ray to gastrointestinal disease (1905) the pendulum swung to the opposite extreme, the effort being made to interpret most gastric phenomena from an organic viewpoint, particularly ulcer, ulcerations and duodenitis.

Today we are at the parting ways of a new concept, or at least of a revised or revived explanation of those gastric disorders of vague origin which, below the level of gross pathological recognition, call for clinical interpretation.

The invention of the ingenious and safe flexible gastroscope by Schindler has reopened this phase of investigation. With the introduction of this instrument and its capable use by experienced manipulators, a whole field of hitherto acceptable concepts has been reopened for re-

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vision and renewed critical analysis

One of the most important contributions of the gastroscopists has been the reawakening of our knowledge of gastritis. While surgeons, pathologists, and clinicians such as Konjetzny, Puhl, Henning, Gutzeit, Hurst and others have studied morphological gastritis in its relation to ulcer and carcinoma without arriving at more than debatable and uncertain conclusions, the gastroscopists have defined for us a gastritis which to them is a disease, not necessarily associated with other pathological changes, one with a clinical symptomatology which is offered to us as, in itself, an explanation of subjective phenomena and of visceral manifestations.

The gastroscopist sees with his instrument changes in the gastric mucosa which are real enough, of marked superficial congestion with edema, occasional hemorrhagic areas, surface erosions and increased mucus production. The process may be hyperplastic and productive in nature or may proceed to the stage of atrophy.

As old-school clinicians we are asked to accept these visualized pictures as representing a disease entity, as such, we ask, is there an associated recognizable clinical picture? Is there a corresponding histological change in the mucosa? Does the process lead to characteristic secretory changes? Can one diagnose or recognize or treat a case of chronic gastritis if one be deprived of the gastroscope and has to rely only on other diagnostic equipment?

Conceding gladly and ungrudgingly the surface changes seen through the flexible instrument, do these manifestations explain the pathological and clinical concept of a gastritis?

#### PATHOLOGICAL DATA

To what extent does histology of the stomach mucosa parallel the gastroscopic observations? The literature, extensive as it is, fails to answer this query. In fact, the dearth of studies on microscopic pathology is bemoaned by Henning, as well as by Schindler himself, both of whom express the hope that studies of this nature will in the near future be carried out by painstaking investigators. The real handicap lies in the fact that biopsies are not possible with the closed lens system of the flexible instrument, nevertheless such studies are possible and are being carried out by a group at the Mt Sinai Hospital who, having in a preliminary examination subjected the patient to a gastroscopy, now proceed

to a minute histological survey of the resected specimen, closely following such an examination

Allowing for our modest inexperience in comparison with such a master gastroscopist as Schindler, and taking into consideration the fact that most of the cases were subjects of benign ulcers, we may still hazard a preliminary impression regarding the parallelism between the gastroscopic visual report and the histological analysis of the specimen

In general such parallelism is inconstant. Frequently when hypertrophic, or less often, atrophic changes are seen with the gastroscope, but little morphological disturbances of structure are visible. Or, when a comparatively normal mucosa is seen, rather advanced infiltration with round cells and plasma cells and eosinophiles may be noted, even to polymorphonuclear invasion. In some instances the parallelism is good, a gastritis is seen grossly and an infiltrating congested mucosa is observed microscopically. In others, all parallelism is absent.

One of the greatest drawbacks in the whole issue is the lack of knowledge regarding what constitutes a normal mucosa, and what changes can be expected in the mucous membrane of individuals who are advanced into the later decades of life. Practically speaking, one rarely sees histologically a normal human mucosa without some cellular infiltration of the mucous membrane. Normal control specimens of mucosa are missing and slides devoid of some cellular hyperplasia or atrophy are to all intents and purposes absent. Some cellular changes characterized by round cell and plasma cell infiltration and connective tissue proliferation are commonly found in other viscera of the adult body, such as the appendix, liver, pancreas and kidney, and yet such changes are not regarded as coming within the realm of clinical consciousness.

By what yardstick are we to determine when a gastritis by microscopy is a gastritis by clinical definition? In the more advanced and severe grades of gastritis the gross specimen with its hyperplastic changes, marked thickenings, prominent gastric areas, even to the stage of *état mamelonné*, may be easily recognizable, as it is to the gastroscopist, and readily verified by the microscope as an advanced gastritis, but the less developed and subtler changes of the mild fundal and corpus gastritis may confuse the gross pathologist, as it may the gastroscopist. It is in these milder and less advanced instances that the histological verification may contradict the gastroscopist's findings.

## SECRETORY CHANGES

There are no consistent variations in the secretory titer that characterize the various forms of gastritis in their milder degrees. All writers agree that no form of gastritis, except the advanced type of atrophic gastritis with its associated achylia, has a pathognomonic change in the secretory acidity or in its morphological constituents (Simpson<sup>1</sup>). We have similarly failed to find a hyperacidity or a hypoacidity that can be predicated upon either the gastroscopic picture of a gastritis or upon a histological change in the cellular arrangement of the mucosa. Not that such a microscopic picture must be demonstrable to parallel secretory variations, but the difficulty of drawing up a clinical syndrome is enhanced by the absence of consistent findings in either the gastroscopic or the histologic picture and the presence of wide variations in the secretory composition.

## X-RAY EVIDENCE

The radiographic evidence of gastritis is similarly confusing. The hypertrophied rugae demonstrable in the mucosal pattern of some stomachs are not a consistent sign of hyperplastic gastritis, nor are the prominent gastric areas and mottling demonstrated by Berg<sup>2</sup> and by Henning and Schatzki,<sup>3</sup> nor the worm-like arrangement of the antral rugae of Gutzeit<sup>4</sup> sufficiently convincing to allow one to draw the conclusion of the presence or absence of a mucosal gastritis. By general agreement (Schindler and Templeton,<sup>5</sup> Henning,<sup>6</sup> Schloss, Ettinger and Pratt<sup>7</sup>), radiography unsupported by gastroscopy is inadequate to determine the presence of a gastritis.

On what basis then may one formulate a clinical picture of gastritis? If histological control norms are absent, if the changes in the microscopic morphology do not consistently parallel the observed gastroscopic findings, if no secretory or radiographic picture characterizes the disease, then only the gastroscopic picture and the subjective complaints of the patient remain upon which to build. A clinical syndrome that demarcates gastritis is concededly absent, the various other forms of chronic gastritis are said to be accompanied by epigastric pain worse after meals, the absence of night-pain, nausea, vomiting, occasional hematemesis due to surface erosions, and general symptoms such as dizziness, vertigo, weakness, loss of appetite and of weight. A characteristic sensitive area has been described by Schindler<sup>5</sup> in the left periumbilical area as character-

izing hypertrophic gastritis

Such symptoms are not mild, but are severe to a degree, and must be correlated as effect to cause with the gastroscopic picture Beaumont,<sup>9</sup> whose opportunity and genius were unexcelled, says "Diseased appearances similar to those mentioned above, have frequently presented themselves in the course of my experiments and examinations. These morbid changes and conditions are however seldom indicated by any ordinary symptoms or particular sensations described or complained of, unless when in considerable excess or when there have been corresponding symptoms of a general affection of the system." Eusterman<sup>10</sup> clearly states that changes in the mucosa do not give rise to clinical symptoms, except occasionally epigastric distress or hemorrhage, thus differing with both Knud Faber<sup>11</sup> and Henning.<sup>12</sup>

If one could dispense with the demand for a histological basis of a disease, as well as with the secretory and roentgenological evidence of a process, one might be willing to interpret the gastroscopic picture in the light of a functional, rather than an organic disturbance. A subpathological entity gives rise to a subclinical picture, in which mucus production, severe congestion even to hemorrhages and motor spasm of long duration eventually lead to cellular changes. Similar disturbances in the nature of pathological physiology characterize some very severe diseases, such as mucous colitis, or chronic rhinitis, or allergic manifestations, diseases with well defined symptomatology, with minimal mucosal changes, but which eventually may lead to mucosal hypertrophy, polypoid formations or atrophic sclerosis.

The constant association of gastritic changes with nervous phenomena such as dizziness, depression, weakness, sense of fullness and insomnia might lead one to invoke a psychogenic or a neurologic factor as the responsible causative agency. Such nervous influences might well induce pathological disturbances of physiology to so great an extent as to produce functional and hyperemic congestive states in the stomach, which would be evident instrumentally but yet not produce organic mucosal changes.

Certainly the theory of Knud Faber<sup>11</sup> who attributed gastritis to previous general infections such as diphtheria, influenza or tuberculosis is hardly a convincing hypothesis, nor has it received general credence. If hasty eating, bad dentures, excessive quantity of ailments and too hot or too cold foods are the proper causative factors, then gastritis is or

should be the most common disease from which all of us suffer, which of course gastroscopically appears to be the fact. In truth, Gutzeit<sup>4</sup> said long ago that gastritis is the most universal of human ailments.

### RECOGNIZABLE FORMS OF GASTRITIS

The difficulty with drawing up a clinical picture that will fit into the pattern of chronic gastroscopic gastritis should by now be evident. But, doubt as one may the significance of the interpretation of what one sees instrumentally, certain well defined and advanced forms of gastritis deserve very definite consideration.

The association of the so-called giant rugae on the greater curvature of the stomach with hypertrophic gastritis has received much attention. The gross crenelation of the border of the greater curvature simulating an early neoplastic defect, the distortion and erasure of the outermost folds and the undue prominence and exaggeration of the lateral and longitudinal folds of the fundus and corpus have frequently been interpreted as being based upon a hyperplastic gastritis with edema, congestion and broadening of the base of the folds as evidence of a disease process. This picture has been dealt with by Kantor,<sup>13</sup> Forssell,<sup>14</sup> L. G. Cole<sup>15</sup> and others. It is truly a very confusing radiographic phenomenon, one which requires accurate knowledge and interpretation to prevent the mistake, either of operating upon a supposed carcinomatous defect of the greater curvature, or of failing to explore a positive and deserving case on the hypothesis that the defect is to be interpreted as a chronic hyperplastic gastritis.

We have had experience with eight such cases, in which the symptoms consisted of abdominal distress, epigastric pain, anorexia, loss of weight and occasionally even a severe anemia. The course was usually a short one of a few months or years which, associated with the greater curvature defect and the exaggerated folds, cleverly simulated a neoplastic infiltration. Six of these cases were operated upon and explored. In three instances the greater curvature wall was reported as thickened or diffusely indurated, in three others the stomach was normal by palpation. Fortunately biopsies were taken in the first three instances in an attempt to define the underlying pathological process. On inspection at the operating table the mucosa appeared cobblestone in appearance, huge cerebriform gyri were present, the rugae thickened, mucosa not abnormal in appearance. The histological appearance of the three

mucosa is in general thickened and hyperplastic, often to the point of actual polypoid formation, the polyp or polyps projecting from a broad base simulating a neoplastic degeneration

At other localities, areas of atrophic mucosa are seen representing an end stage of atrophic gastritis. The surface of the rugal folds may show superficial minute erosions or larger discrete ulcerations with rounded overhanging edges which, with the gastroscope, appear turgid and congested and easily friable. The submucosa is often enormously thickened like that of a *linitis plastica*, the muscularis propria is hypertrophied to a width several times its normal depth and resembles the benign hypertrophic pyloric stenosis described in the literature (Boas,<sup>19</sup> Konjetzny,<sup>16</sup> Cruveilhier<sup>20</sup>)

Histologically, the mucosal thickness which is normally 12 to 14 millimeters in cross-section may be two or more times that diameter so that with the submucosal and muscular hypertrophy the whole simulates a new growth or a pyloric hypertrophy of organic origin

The symptoms which accompany so definite a pathological process are equally definite. They simulate the picture of a benign ulceration of the prepyloric or antral region, only the gastroscope or an exploratory operation being capable of differentiating the conflicting symptoms. Pain and heartburn are the outstanding features in the ulcer-like cases, nausea and vomiting and weight loss those of the carcinoma-like instances. The epigastric distress and pain with anorexia and heartburn are usually more continuous than in ulcer, periodicity is lacking, the course is more rapid and severe and the general loss of weight and strength, more significant

High normal or hyperacid secretory curves accompany the ulcer type. The gastroscopic examination usually shows an edematous, thickened mucosa, marked congestion, single or multiple superficial ulcerations with occasional deep penetrating Dieulafoy type of erosion. Healing of these ulcerations may be observed at successive gastroscopies. In one patient resection was done under the mistaken impression that he had a neoplasm. The mucosa when seen grossly was cobblestone in appearance and resembled the mottled areas described by Schatzki with spot radiographic films. Histologically a diffuse polypoid infiltrating gastritis of all the walls of the antrum was seen (Figures 1 and 2)

In these cases radiography is usually insufficient to differentiate these benign from potentially malignant conditions, an antral defect is per-

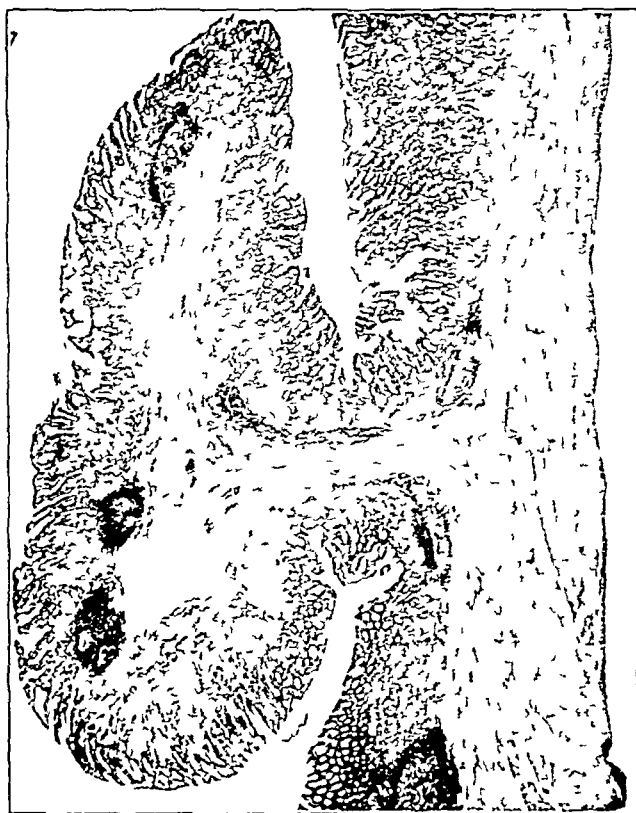


Fig. 1—Polypoid antral gastritis

sistent and repeatedly demonstrable, the presence of the severe gastritis and of deep erosions throwing the antrum into spasm simulating a neoplastic defect<sup>18</sup>

The type of case resembling from its initiation the picture of an antral tumor as described by Florcken<sup>21</sup> is still more confusing (Table III). In this group anorexia, vomiting, epigastric discomfort and a rapid and severe loss of weight are alarming and progressive features. The course is one of months rather than years. Anacidity is the rule though two of the five cases had low normal titers. Hematemesis and melena occur, though infrequently as seen in the literature (Benedict<sup>17</sup>), one of our cases showed gross bleeding. The vomiting may well simulate that of true pyloric stenosis due to a cicatrizing duodenal ulcer. The hypertrophy of the pyloric and antral musculature is sufficiently obvious in the resected



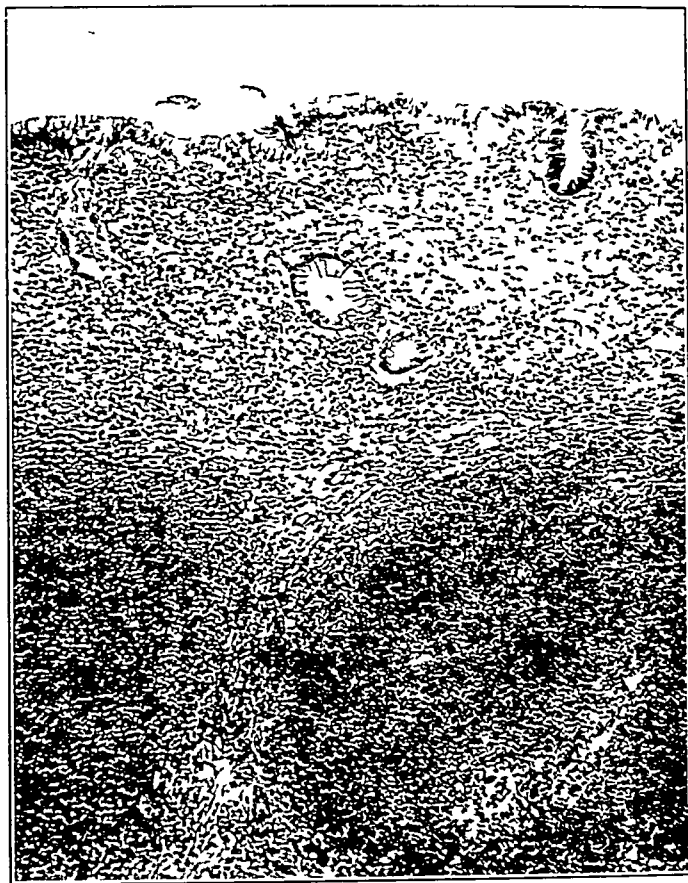


Fig 2—Severe atrophic gastritis with intestinal metaplasia of the surface epithelium

specimen to explain the persistent emesis (Figure 3) Radiography demonstrates a filling defect of the antrum with prepyloric narrowing, lengthening of the pyloric canal (Kirklin and Harris<sup>22</sup>), infiltration of lesser and greater curvatures of the antrum and occasionally a true polyp formation as evidenced by an enduring luminosity or area of lesser density in one spot of the antral wall

All of the five patients were subjected to resection under the impression of malignancy, all of them in the pregastronomy days The gross specimens showed marked and tumor-like thickening of the antral walls, polypoid mucosal hypertrophies, and a rigid thickened pylorus

The etiology of antral gastritis is not clear Alcohol cannot be indicted, nor do nutritional factors, faulty dentition, previous infections



Fig 3—Antral gastritis with marked hypertrophy of the pylorus

TABLE III

## ANTRAL GASTRITIS—SIMULATING CARCINOMA—RESECTIONS

NO	NAME	AGE	HISTORY	ACIDITY	X RAY	OPERATIVE FINDINGS	HISTO-PATHOLOGY
1	SB	67 F	5 months vomiting loss weight	0-10	Filling defect lesser curve antrum	Gross thickening antral wall serpiginous ulcerations	Atrophic Gastritis erosions, thickening of submucosa and muscularis
2	HS	57 F	3 months anorexia vomiting	0-12	Antral defect	Marked thickening of wall polypoid mucosal hypertrophy	Severe acute and chronic Gastritis
3	HO	45 F	3 weeks nausea epigastric discomfort	16-45	Pyloric narrowing	Thickened pylorus antrum 3 times normal	Chronic Gastritis edema of submucosa tremendous hypertrophy of muscularis
4	MR	46 F	months anorexia - 44 weight loss 10 pounds	26-46	Pyloric irregularity	Tumor-like thickening antrum submucosa muscularis	Chronic Gastritis atrophy of glands tremendous hypertrophy of muscularis
5	LK	35 M	4 yrs epigastric pain	0-8	Multiple contracting lesions antrum polypoid gastritis	Cobblestone mucosa small polyp	Severe acute and chronic atrophic Gastritis

nor unhygienic eating habits seem to be sufficiently unusual or potent to give rise to so severe a lesion. In spite of its severity, the course and prognosis of antral gastritis is relatively benign. The ulcer-like cases react well to restricted modified Sippy diet and alkalis, together with bed rest and change of habits of life. Rest and recreation are essential. We have used no gastric lavage though Hurst is enthusiastic about the employment of dilute hydrogen peroxide. Various bland medicaments have been recommended by others. The recognition of the disease process clarifies the problem. Here one leans most heavily on the gastroscopist, for on him falls the task and responsibility of differentiating the benign from the malignant and of outlining the therapeutic schedule.

Presumably even in the benign cases with polypoid formation and pyloric hypertrophy and stenosis, resection will at times become essential. Perhaps, with more popular and universal use of the gastroscope, earlier recognition of the cases will obviate extensive surgical procedure.

### CONCLUSIONS

We have observed that the gastroscopic picture of a chronic gastritis with difficulty is associated with any known histological change in the mucosa, and that secretory and radiographic diagnostic features are missing. Only with hesitation may we draw upon a clinical symptomatology that will express in pathognomonic or even suggestive manner the meaning of hyperplasias and atrophies seen through the flexible instrument. Yet, in its advanced stages we recognize with facility a type of antral gastritis that is well defined, that has clear-cut though not distinguishing characteristics, a persistent radiographic defect, and often secretory deficiencies.

Is this latter picture the end-stage of all those less well-defined appearances that the gastroscopist terms chronic gastritis? Or, is that which he sees merely a pathological deviation of function that is subclinical and lacking in a true morphological substratum?

For decades no clinician has ventured the clinical diagnosis of chronic gastritis. Today, a gastroscopist as well-known as Gutzeit declares that gastritis is probably the most common disease of mankind. The transition is too radical and extreme to permit such a reversal of all previous concepts without deliberate and cautious study, not only by the instrumentalist but by the body of observing physicians and pathologists.

Let us ask more time and more experience so that, with sound judg-

ment, we may recognize the outstanding features of a clinical syndrome and its course and progress before we formulate conclusions regarding the significance of these visual observations. At the same time, the recognition of the well-defined end-picture of antral gastritis, with its medical and surgical and diagnostic difficulties, calls for further research, more education and a greater diffusion of the knowledge derived from this study. Throughout, we depend upon the gastroscopist, for in his vision and perspicacity, and in the correct reporting and interpretation of his findings lies the future of the subject.

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## VITAMIN A WITH SPECIAL REFERENCE TO THERAPY\*

ARTHUR M YUDKIN

A CRITICAL REVIEW of the advancement of science reveals the startling fact that the knowledge of nutrition has played an important role in the development of modern medicine. At no period in the history of science has the progress of medical knowledge been so swift as in the last quarter of a century. The valuable contributions from the laboratories of Osborn and Mendel<sup>1</sup> and McCollum and Davis<sup>2</sup> were among the first in the present era of vitamin therapy. Their contributions inspired other laboratory workers who in turn helped implant more firmly the idea that diseases may be due to dietary deficiencies.

It was not until the fundamentals of an adequate diet were demonstrated that a relationship between faulty diet and the so-called deficiency diseases could be demonstrated. When the more important clinical manifestations of the disturbance are present it is not difficult to diagnose a deficiency disease.

It seems almost unbelievable that this condition should prevail in the United States where it seems reasonable to believe that the majority of the people receive enough of the food accessory factors in their daily diet to ward off a vitamin deficiency. Nevertheless, we are confronted with reports of borderline cases or subclinical states of dietary deficiencies. It is possible that these conditions are more readily detected because of the better understanding of the subject and because of their similarity to some of the disturbances produced experimentally in the laboratory animal by deficient diets.<sup>3</sup> It has also been observed that qualitative and quantitative errors in the diet frequently play a tremendous part in the etiology of human illness. It is noteworthy that vitamin deficiency occurs in all ages and is not confined to the poor classes but can and does occur even in prosperous communities.

To the clinician it may seem rather improper to interpret the afflictions of the human body largely in terms of pathologic findings observed

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in laboratory animals on special deficiency diets, but to one who has had the privilege of practicing medicine and participating in laboratory experimentation as well, it is understandable that use be made of this method of comparison. It is not altogether satisfactory from a scientific point of view to study large groups of people subsisting on poor diets, for under ordinary circumstances a diet deficient in one vitamin is likely to be unbalanced with regard to other vitamins, minerals, and basic food factors. It therefore became necessary to resort to experimental investigation for this knowledge.

Sufficient experimental evidence is at hand to warrant the conclusion that vitamin A is very essential for the maintenance of a satisfactory state of nutrition, normal growth, and health at all ages. Furthermore, Sherman<sup>4</sup> and his co-workers have reported that frequently a proportion of vitamin A in the food, sufficient to support normal growth and maintain every appearance of good health for a long time, may still be insufficient to meet the added nutritive demands of successful reproduction and lactation. Such observations as these emphasize to the clinician and student of nutrition alike the importance of ascertaining what constitutes the optimal intake of the various dietary essentials under all conditions of life. There should be greater emphasis placed on the optimum as contrasted with a merely satisfactory diet. Evidently a diet may be satisfactory, yet fail in some measure to meet the needs of the organism.

### THE NATURE, PHYSIOLOGY AND SOURCES OF VITAMIN A

From the early experience with vitamin A and the substances having a vitamin A effect it was noted that several forms of precursors must be present in nature.<sup>5</sup> Foods having a yellow or green color are generally rich sources of this vitamin. In plants the vitamin activity was traced to the presence of carotinoid pigments. These pigments seem to be closely associated with chlorophyll in plant life. It has been shown that the quantity of chlorophyll may be considered as an index of carotene content of green plants. It was also observed that natural yellow color may be a rough qualitative guide for the selection of vitamin A active animal products for it seems to indicate the consumption of carotenoids and vitamin A precursors by the animals. If the animal is capable of transforming carotene to vitamin A the fatty animal products are apt to contain some vitamin A regardless of the color of the product, some

products may even be exceptionally rich in vitamin A and relatively poor in pigment. Certain of the fish liver oils have this characteristic, notably that of the halibut and the burbot.

Vegetable carotene is usually present in nature as a mixture of several forms. These have been classified as alpha, beta, and gamma carotene. The only other substance found to behave like the carotenes in acting as a precursor of vitamin A is cryptoxanthin. The carotene which seems to bear the closest chemical and biochemical relation to vitamin A is the beta isomer. The chemist tells us that it is a nitrogen free, aliphatic, methylated polyene having two identical, unsaturated, methylated terminal rings. By comparing the formula for vitamin A with that for beta carotene it may be pointed out that the one molecule of beta carotene gives rise to two molecules of the primary alcohol vitamin A. In spite of the accumulated circumstantial evidence pointing to its actual chemical configuration, it is still important for science that the natural vitamin A be isolated in pure form and made available for clinical use. There are some recent reports<sup>6</sup> indicating that this has been accomplished but as yet they have not been confirmed. Similarly the conversion of carotene to vitamin A has not yet been accomplished by chemical procedures. *In vivo*, however, the liver is accredited as the site for the formation of vitamin A in animals but the detail of the process has not been elucidated.

It is known that a considerable amount of the ingested carotene appears in the blood and is deposited in the adipose tissue of man and animal. It has also been shown that after carotene is absorbed into the thoracic duct it is found in the liver. When a colloidal aqueous suspension of carotene is injected into the portal or systemic circulation it is rapidly removed from the blood stream by the reticulo-endothelial system. It has been suggested<sup>7</sup> that the liver cells are necessary for the conversion of carotene to vitamin A by the fact that the conversion is decreased by phosphorus poisoning,<sup>8</sup> and in certain diseases of cattle which involve the parenchymal cells, carotene remains unconverted in large quantities in the Kupffer cells. It is known that vitamin A may disappear from the blood during starvation and during infection, even though considerable stores may remain in the liver.

According to Clausen<sup>9</sup> the vitamin A of natural oils and fats occurs as an ester, in preparations made by saponification it occurs as a free alcohol. When the vitamin was administered as a free alcohol it was found in the lymph mainly in the esterified condition. It therefore appears

that the mechanism of absorption of vitamin A includes linkage with fatty acids probably in the intestinal wall. Such linkage is impossible in the case of the hydrocarbon carotene, a fact which may explain its lower coefficient power of absorption. There is evidence that the vitamin is absorbed as a bile acid compound, transported in the blood and lymph as a fatty acid ester, and stored in the liver as a similar compound. This suggests that the vitamin performs its biochemical function in chemical combination with other substances rather than as a free substance.

Vitamin A and its precursors exhibit characteristic differences in absorption from the intestinal tract and certain physiologic conditions have been reported which alter the utilization of vitamin A and its carotene precursors. It is known that bile is essential for the utilization of carotene but apparently not for the utilization of vitamin A, for if bile is shunted from the small intestine to the colon, the utilization of carotene is prevented. It has been shown that liquid petrolatum does not interfere markedly with absorption of vitamin A from the intestine but does inhibit the absorption of carotene. The composition of the diet other than its vitamin A content, has been reported to affect the absorption and utilization of both vitamin A and the precursors called provitamin A. Absorption and utilization of vitamin A and carotene are affected by the quantity administered and the manner of administration, and the general physiologic conditions of the alimentary tract.

#### STORAGE OF VITAMIN A IN THE BODY

Experimentally it has been shown that most animals have a remarkable capacity for the storage of vitamin A. It is rather significant that most of the accumulated vitamin A in the body is present in the liver and small amounts appear in the lungs and the kidneys. It has been estimated that the vitamin A concentration of the liver of man, the rat, and cow on a normal intake is from 10 to 20 mg. per hundred grams. The vitamin A content is much lower in the liver at birth than in the liver of the normal adult. Thus it would seem that the accumulation of vitamin A in the liver tends to increase with age. The amount present is dependent on the character of the diet. The surprisingly low reserve of vitamin A in the newborn makes plain the necessity for an adequate intake of vitamin A during infancy.

The rat may in a few days store enough vitamin A to supply its nutritional requirements for several months. In times of low intake this store



is used to supply physiologic needs. It has been noted that during a prolonged deficiency the reserve is gradually depleted, normal cell functions are suspended, and pathologic change develops. Chronic diseases and infections seem to lead to slightly lowered vitamin A reserve. It is assumed that this takes place because of reduced intake of vitamin A or of decreased assimilation in the alimentary tract and increased metabolic demands.

### THE STABILITY OF VITAMIN A AND CAROTENE

Then the question arises as to the stability of these vitamin A values. It has been amply demonstrated that the physiologic activity of both vitamin A and carotene may be rapidly destroyed at high temperatures when oxygen or an oxidizing agent is present. According to Eddy and Dalldorf<sup>10</sup> the stability of any source of vitamin A will depend on the exposure of the vitamin or provitamin to oxidizing factors, to the presence or the absence of protecting factors, such as anti-oxidants in the holding source, or to the skill of the manufacturer in avoiding the action of oxidation in the preparation and merchandising of the vitamin sources. Practically all plant sources and animal sources show progressive destruction of the vitamin A during storage unless measures are taken to prevent fermentation and oxidation. Frozen products, however, seem to retain their vitamin A value well, whereas dehydration may be destructive to vitamin A unless quick drying to inactivate enzymes is utilized to prevent the destruction. Heat treatment in ordinary cooking operations appears to destroy little of the vitamin A value, perhaps because the carotene is less labile in plant tissues than is vitamin A itself. It is not readily affected at the ordinary temperatures of boiling and baking but is destroyed at high temperatures such as those obtained in frying. It is said that the destruction of vitamins is less when foods are heated at high temperatures for short periods than when they are heated at low temperatures for long periods. Although vitamin A is only slightly soluble in water, only small quantities of water or no water at all should be used in cooking. Steaming is one of the preferred methods for cooking, since the time required is short and the amount of water used is small.

### EXPERIMENTAL OBSERVATIONS

It is evident from the early animal experimentation that there must be some relation between vitamin A deficiency and poor dark-adaptation

of the eyes<sup>11</sup> At first it was difficult to understand what part vitamin A played in the process until it was disclosed that the rate of regeneration of visual purple after its bleaching by a bright light in the living animal was less in the rats receiving the deficient diet than in the controls<sup>12</sup> Pathological changes were observed at the chorioretinal junction (layer of Brucke) of the eyes removed from these animals<sup>13</sup> It was shown that the fat extracted from normal retinæ (of several species) is one of the richest sources of vitamin A substances<sup>14 15</sup> This finding suggested the possible relation of the vitamin A content of the retina and visual purple Wald<sup>16</sup> succeeded in demonstrating in animals, birds, and amphibians that vitamin A was the prevailing substance in the extracted material of the retina He also observed that visual purple on bleaching yielded a carotenoid which he called retinene Retinene under certain conditions changed slowly to vitamin A and more rapidly to visual purple On the basis of these observations Wald developed an equation which sets forth certain speculations on the chemical reactions which might take place in the rod and cone layer of the retina during dark-adaptation after the ocular tissue had been previously exposed to light

A similar observation was made by Kuhne<sup>17</sup> some sixty years ago when he noted that the visual purple in rat and rabbit retinæ may be synthesized in two ways — a slow process in which the visual purple was developed from newly supplied materials, and a more rapid one in which the photoproducts of the stimulated retina were the starting point Until recently the variation of the visual threshold in dark-adapted eyes was attributed to changes in the rods alone, but Hecht and his co-workers<sup>18</sup> demonstrated that the cones likewise play a significant role in this visual cycle They conclude<sup>19</sup> from a study of thirteen persons afflicted with chronic liver disease that there is a true parallelism in the behavior of cone and rod thresholds in dark-adaptation and its response to vitamin A therapy

A survey of old records reveals the frequent association of ocular diseases with famines caused by drought or war Ophthalmologists have repeatedly attributed night blindness or hemeralopia xerophthalmia corneal lesions and several forms of chorioretinitis to faulty nutrition These eye disturbances in man result from conditions so complicated that it is not possible without further evidence to attribute all of them to a specific starvation of a single vitamin However outspoken vitamin A deficiency in man appears to have been somewhat more common in

Europe and Asia than in this country. Recent studies in the United States would seem to indicate a surprising prevalence of subclinical vitamin A deficiency, particularly among children.<sup>20</sup> The diagnosis is based on the assumption that individuals who show poor dark-adaptation have a vitamin A deficiency.

Dark-adaptation is the change in light sensitivity which the eye undergoes in the dark following a stay in the light. It is an established clinical experience that hemeralopia may occur in poorly nourished persons and that great mental or physical exertion and exposure to glaring light may bring on the condition or aggravate an existing hemeralopia. Since dark-adaptation is mainly a phenomenon of rod and somewhat of cone function and is associated with the regeneration of visual purple, investigators have applied various means for the measurement of the rate of dark-adaptation to the problem of estimating vitamin A requirements of human beings.

These several methods which were recently described in special articles in the *Journal of the American Medical Association*<sup>21</sup> involve a principle which is common to all, namely, the measurement of the power of the eyes to adapt themselves to dim illumination. Some of these instruments are very simple while others are too complicated to be applied in routine clinical examination. As yet no one instrument fulfills all the necessary refinements for the measurement of dark-adaptation in people of all ages.

Clinical experience leads me to believe that there are several factors which may influence dark-adaptation, for instance, using the fundus oculi as a criterion, true light complexioned individuals (blonds) seem to have a different norm from that of the dark complexioned individuals (brunets), prolonged dark-adaptation is present in a variety of diseases, e g, retinitis pigmentosa, retinitis albescens, choroideremia, glaucoma, and many others. It is important to point out that night-blind persons show poor dark-adaptation but poor dark-adaptation does not signify night blindness. In the latter instance the poor dark-adaptation comes on after exposing the retina to bright light. This is probably the condition that we are dealing with in vitamin A deficiency. There is another type of retinal disturbance which is called "glare-blindness," a condition which is often considered as nyctalopia in contrast to the condition of poor adaptation to dark known as hemeralopia. This also has been alluded to as a vitamin A deficiency.

## CLINICAL OBSERVATIONS

Vitamin A deficiency is practically unknown in nurslings, nevertheless, when the mother suffers from malnutrition, the nursling will also present manifestations of deficiency disease. The usual history of this type of disturbance reveals that the infant has been fed on a diet containing either insufficient milk, prepared milk, or no milk products at all over a period of at least one or two months, in many instances a digestive disorder may precede the onset of symptoms resulting in a diminished food intake together with imperfect absorption of the food consumed. Simultaneously there is a failure to gain in weight, and this may be followed by an actual weight loss. The normal activity of the child is diminished. The skin may become dry and scaly. In older children the eyes may show a viscid, stringy conjunctival secretion, matting the lids together. When the discharge is removed the cornea is clear and the conjunctiva is not congested. There is present, a marked photophobia and blepharospasm which is aggravated by exposure to light. As the condition progresses, a dryness of the bulbar and palpebral conjunctiva takes place with a typical Bitot's plaque adherent to the exposed conjunctiva of the eyeball. The cornea may now show small single or multiple ulcers which, if unchecked, go on to perforation of the cornea. Sooner or later hypopyon may result. In older children the eye condition often does not progress beyond a xerosis conjunctivae, and corneal destruction is less frequent even with a long period of vitamin starvation. In infancy the course of the disease is more rapid. This may be due to the greater need of the vitamin for growth. As the disease progresses, intercurrent infections of the skin, lungs, and urinary tract may occur, and finally the condition may terminate in bronchopneumonia or a diarrheal disorder.

Characteristic lesions of the human skin have been attributed to vitamin A deficiency. The lesions usually occur in sexually mature persons between sixteen and thirty years of age. They are much more frequent in men than in women. The disturbance appears first on the anterolateral surface of the thighs and posterolateral portion of the upper forearm and later spreads to the adjacent areas of the skin. The lesion consists of small pigmented papules at the site of the hair follicles. At first they appear as papules with keratitic plugs, later some of them develop into pustules. The skin is dry and scaly. Atrophy of the sweat glands and keratinizing metaplasia of their ducts are responsible for the

condition There is a general increase in the pigmentation of the skin

It has been suggested that gastric ulcers may be associated with vitamin A deficiency, but this condition is rather rare in the laboratory animals and in man Likewise it has been said that diets deficient in vitamin A may cause urinary calculi This assumption was based on the presence of urinary stones in experimental animals deficient in vitamin A and D and unbalanced in mineral content This finding has not been corroborated by most investigators Clausen<sup>9</sup> points out that although urinary calculi may be produced in experimental animals by feeding special diets, the factors involved are not yet clearly defined

Although the vaginal mucous membrane becomes permanently cornified in animals deprived of vitamin A and the vaginal smear may be used as a method for the detection of the deficiency, the effects of moderate deficiency of vitamin A on fertility in man are unknown Bessey and Wolbach<sup>7</sup> however, believe that atrophy of the testes and keratinizing metaplasia of the uterine mucosa may be expected in human adults

### PROPHYLAXIS

It is apparent that the prevention of A-avitaminosis depends upon two factors the supplying of a sufficient quantity of vitamin A in the diet of the individual and the proper absorption of this factor How much vitamin A is necessary for the maintenance of normal growth and health in the individual? We have as yet insufficient knowledge of the amount of vitamin A in the diet requisite for health However, several investigators have made measurements of the minima for different species of laboratory animals and these might be regarded as offering suggestion Cowgill<sup>22</sup> suggests that at least 400 international units per 100 calories per day is necessary for a child This is based on the consideration of the maximum amount of vitamin A ever found in human milk and the idea that this might be nature's suggestion of an appropriate intake for the infant This would lead one to assume that the ordinary diet contains sufficient vitamin A when cow's milk, butter, eggs, and certain vegetables and fruits are included One must remember, however, that cow's milk may have a seasonal variation in its vitamin content dependent upon the diet of the cow Since cow's milk runs about one-tenth to one-quarter of vitamin A value as compared with human milk, and cow's milk is the chief component given babies, it is obvious that there is justification of feeding vitamin A to the infant The administration of one to two tea-

spoonfuls of standard cod-liver oil daily, will amply protect against any vitamin A deficiency no matter what the child's diet

Harris<sup>23</sup> placed the minimal daily requirement at 1,000 units (U S P ) Jeghers<sup>24</sup> estimated that 4,000 international units of vitamin A daily represents the minimal requirement for a healthy adult Growing children should be allowed twice this amount Cameron<sup>25</sup> advised an optional intake of 5,000 units According to Guilbert, Miller and Hughes<sup>26</sup> a level of vitamin A or carotene intake which is just sufficient to prevent gross signs of hemeralopia suffices also for excellent gains in weight and for maintenance of a thrifty physical appearance of animals for indefinite periods, although the storage of the vitamin in the body may be very meager indeed These workers report that several species of animals (cattle, sheep, and swine) differing widely in body weight showed almost identical requirements for vitamin A or carotene per kilogram of body weight for the prevention of hemeralopia

It is estimated that the foods recommended by the Health Committee of the League of Nations<sup>27</sup> would approximate a daily intake of 2,000 to 4,000 units for an adult and at least 5,000 U S P or international units of vitamin A for the pregnant and nursing woman and 6,000 to 8,000 units of vitamin A daily for growing children

The mere recital of these many figures emphasizes the fact that we are becoming reasonably quantitative in our approach to this problem There may be some disagreement as to the exact requirement, but time will no doubt resolve this controversy Inasmuch as the vitamin appears to be nontoxic, the clinician need not be unduly concerned if he chooses to give doses well above even the highest estimates just cited

## TREATMENT

Obviously two lines of therapy suggest themselves (1) the use of a high vitamin A diet, and (2) the administration of the concentrates or the pure substance in large doses Inasmuch as the relief of deficiency symptoms seems quite definitely related to the amount of the needed factor supplied, up to the ability of the organism to utilize the vitamin, it is evident that the use of a high vitamin diet is of value chiefly in prophylaxis and in support of other therapy It would probably be impossible to give the most effective therapeutic dosage simply by feeding an excellent diet The use of various concentrates and the pure vitamin, when it becomes available is definitely indicated therefore when marked symp-

toms of vitamin A deficiency appear. Patients suffering from this deficiency disease should be treated with a form of vitamin A that can be completely utilized. When cod-liver oil or other fish oils are not tolerated their concentrates are valuable. Some clinicians use carotene in these cases. In urgent cases where the digestion will not tolerate these substances, it is possible to administer vitamin A by an intramuscular injection of a cod-liver oil concentrate or the pure substance when it becomes available. In the advanced cases which occur so frequently in infancy, the digestion is often disordered and this must be treated carefully in order to allow the proper absorption of the vitamin A administered.

### SUMMARY

It is apparent that vitamin A is a dietary essential, that conditions due to the lack of it occur and that these may be treated by numerous available sources of the vitamin. An attempt has been made to point out the limitations of the present knowledge concerning these conditions and their treatment. Although great progress has been made, with a continuation of research, we may confidently look forward to greater advances in our knowledge in this field.

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WILLIAM HALLOCK PARK

## IN MEMORIAM

## WILLIAM HALLOCK PARK

1863-1939

With the death of Dr William Hallock Park on April 6, there has passed from us a lovable, distinguished and modest scientist whose work in the solution of major health problems brought incalculable benefits to mankind, and shed luster on American medicine.

Born in West Eleventh Street on December 30, 1863, the son of Rufus Park and Mary Hallock Park, Dr Park's entire life was spent in and bound up with New York City and its institutions. At the age of twenty he graduated from the College of the City of New York, three years later he received the degree of Doctor of Medicine from the College of Physicians and Surgeons. Then came an internship at the Roosevelt Hospital, and postgraduate study in Vienna.

On his return from abroad, a modest scholarship placed at his disposal by Professor Prudden enabled Dr Park to undertake a bacteriological study of diphtheria, a study which led to his entrance into the newly established diagnostic laboratory of the Health Department, April 1893. Here Dr Park introduced the serum culture outfits for making throat cultures, a method still used throughout the world. Following the favorable reports concerning the newly discovered antitoxin for diphtheria, Dr Park by the end of 1894 began producing the first antitoxin made outside of Europe.

Realizing that Dr Park was far too valuable a scientist to keep at routine bacteriological work, Dr Hermann Michael Biggs in 1895 established a Research Laboratory, in quarters over the disinfecting station adjoining the Willard Parker Hospital on East Sixteenth Street and placed Dr Park in charge.

In the same year the University and Bellevue Hospital Medical College appointed Dr Park instructor in contagious diseases. Thus began that notable career in teaching which during the next forty-two years influ-

enced thousands of physicians who received their training at that famous medical school, and many other thousands of students who used Dr Park's text book in their study of bacteriology.

Dr Park thus held two positions and did a splendid job in each. In the health department, his direction of the Research Laboratory quickly made it one of the foremost institutions of its kind, while at the medical school he built up an outstanding department of bacteriology and hygiene of which by 1900 he was full professor. In 1933 his title was changed to Biggs Professor of Preventive Medicine and Director of the Bacteriological Laboratory, in which position Dr Park continued until his retirement in 1937.

In 1901, when the New York County Medical Society organized its commission to supervise the production of "certified milk," Dr Park was placed in charge of the laboratory work and field inspection. This marked his entrance into the field of milk sanitation, in which he quickly became the recognized authority. Moreover, as head of the Health Department Laboratories, the experience thus gained with certified milk made Dr Park an invaluable adviser to the Department of Health in its efforts to provide safe milk for New York City.

One often hears efficiency experts say that one cannot hold two jobs at once and do them well. Dr Park's career shows that he always filled more than two and that each contributed to the accomplishment of the other. His teaching at the medical college was undoubtedly better, more practical and more applicable because of his connection with the Health Department. His experience at the College certainly fitted him better to devise means whereby the Health Department could more effectively aid physicians in their work. His experience on the Regents Board of Medical Examiners helped both medical schools and health departments in planning for the teaching of public health and preventive medicine. His connection with

the Certified Milk Commission was of inestimable value alike to physicians, to health authorities and to the milk industry, and finally his prestige as a scientist encouraged financial support of public health and medical education.

Dr Park's laboratory at East Sixteenth Street was the Mecca of scientists from all over the world. And no wonder, for, figuratively speaking, there were no doors to his laboratory. Visitors were always welcome and were never denied the opportunity to observe the work and methods employed, no one went away without having received help and inspiration.

It is impossible in this brief memoir to indicate the enormous influence which Dr

Park's work had in the many fields in which he was active. Diphtheria, typhoid fever, dysentery, tuberculosis, pneumonia, meningitis, rabies, serum concentration, milk sanitation and pasteurization—these are a few of the subjects to which his laboratory made major contributions. Throughout all of Dr Park's work one notes the accuracy and scrupulous honesty in reporting observations, and the insistence of adequate controls for all experimental investigations.

The best and truest memorial to Dr Park is his accomplishment for humanity, and thus we may visualize rather as a living and continuing influence and inspiration than solely the fulfillment of a noble life.

CHARLES F. BOLDUAN

### DEATHS OF FELLOWS

EDGAR, JAMES CLIFTON. Round Hill Road, Greenwich, Connecticut, born in New York City, June 14, 1859, died in Greenwich, Connecticut, April 8, 1939, received from Lafayette College the degrees of Ph B in 1882 and A M in 1884, graduated in medicine from New York University Medical College of New York City in 1885, elected a Fellow of the Academy February 6, 1890.

Dr Edgar was emeritus professor of obstetrics at Cornell University Medical College, consulting obstetrician to Bellevue Hospital and obstetrician to the Manhattan Maternity Hospital and Dispensary. He was a Fellow of the American College of Surgeons, a member of the American Medical Association, the American Gynecological Society, the New York Obstetrical Society and the State and County Medical Societies.

Dr Edgar was the author of a notable book on the practice of obstetrics, and con-

tributed many articles to the literature of his special field.

KENYON, JAMES HENRY. 563 Park Avenue, New York City, born in Cannonsville, New York, July 9, 1872, died in New York City, April 10, 1939, received the degree of B S from Princeton University in 1894, graduated in medicine from the College of Physicians and Surgeons, New York City, in 1898, elected a Fellow of the Academy May 5, 1904.

Dr Kenyon was surgeon to Fordham Hospital, consulting surgeon to Booth Memorial and associate surgeon to the New York Neurological Institute. He was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the American Association for Thoracic Surgery, the New York Surgical Society and the County and State Medical Societies.

PARK, WILLIAM HALLOCK. 333 East 68 Street, New York City, born in New York City, December 30, 1863, died in New York City, April 6, 1939, received the degree of A B from the College of the City of New York in 1883, graduated in medicine from

the College of Physicians and Surgeons in New York in 1886, awarded the degrees of LL.D from Queens University, Kingston, Canada, in 1910, and D.Sc from New York University in 1926, Yale University in 1929 and Columbia University in 1929, elected a Fellow of the Academy April 7, 1892. He was Vice-President of the Academy in 1927, 1928 and 1929.

Dr Park was professor of bacteriology and hygiene at New York University and Bellevue Hospital Medical College, 1897-1937, director of the New York Public Health Department, Bureau of Laboratories, 1894-1937, and its director emeritus since 1937, consulting bacteriologist to the State Department of Health since 1914, and its medical examiner in bacteriology since 1917, consulting bacteriologist to the United States Quarantine Service since 1921 and consulting bacteriologist to the Willard Parker Hospital since 1931.

Dr Park was a Fellow of the American Medical Association, a member of the American Public Health Association and its president in 1923, the Association of American Physicians, the American Association of Pathologists and Bacteriologists, the American Society for Experimental Pathology, and the County and State Medical Societies.

He was the author of a number of books on bacteriology and immunology and a contributor to technical journals on these subjects.

STOCKARD, CHARLES RUFERT 1300 York Avenue, New York City, born in Washington County, Mississippi, February 27, 1879, died in New York City April 7, 1939, received the degrees of B.S. and M.S. from the Mississippi Agricultural and Mechanical College in 1899, and 1901. Ph.D. from Columbia University, New York City, in 1906 and D.Sc. from the University of Cincinnati in 1920, graduated in medicine from the University of Würzburg, Bavaria in 1922.

elected a Fellow of the Academy January 2, 1913.

Dr Stockard joined the Department of Anatomy of Cornell Medical College in 1906, becoming professor of anatomy in 1911, a position which he held until his death. He was also President of the Board of the Rockefeller Institute of Medical Research and conducted cancer research for the Huntington Fund.

Dr Stockard was well known as a lecturer, and among many others delivered the following: the DeLamar Lecture at Johns Hopkins University in 1925, the Harrington Lecture at the University of Buffalo in 1926, the Beaumont Foundation Lecture at Detroit in 1927, the Lane Lecture at Stanford in 1930, the Potter Memorial Lecture at Jefferson Medical College in 1934, and the Joseph Collins Lecture at the Academy of Medicine in 1937.

He was a member of the American Association for the Advancement of Science, the Society of Experimental Medicine and Biology, the National Academy of Sciences, and the American Association of Anatomists, secretary, 1914-22, and its president, 1928-30.

Dr Stockard was the author of a number of books and contributed to many scientific journals. His chief investigations have been on subjects of morphology.

WASHTON, JACOB 940 Grand Concourse, Bronx, New York, born in Russia, September 20, 1889, died in Sarasota, Florida, March 18, 1939, graduated in medicine from New York University and Bellevue Hospital Medical College in 1913, elected a Fellow of the Academy February 3, 1931.

During the World War, Dr Washton served as a major in the American Expeditionary Force. His decorations included the British Military Cross and the French Legion of Honor.

Dr Washton was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

# TWELFTH GRADUATE FORTNIGHT

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<i>Hypo and hyperpituitarism</i>	Leo M Davidoff
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<i>Hyperthyroidism</i>	Harold Thomas Hyman
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1939

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BULLETIN OF  
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JULY 1939

THE SIGNIFICANCE TO MEDICINE OF  
PRESENT POPULATION TRENDS\*

*The Hermann Michael Biggs Memorial Lecture*

FREDERICK OSBORN

WE ARE met to honor the name of one who left his distinguished mark on medical practice in this country. The forward-looking quality of his work is evidence that he would have desired that these lectures should provide from time to time an occasion for the members of his profession to consider the problems created by a changing world. It must have been in the minds of those who proposed the subject of this evening's discussion that Dr. Hermann Biggs would have been one of the first to recognize that the cumulative decline in births in recent years presents new problems and suggests added functions for those engaged in the practice of medicine.

We are at a major turning point in human biology. Following on a period of unprecedented numerical increase, European peoples appear headed for a serious decline. During a million or more years of existence, mankind slowly and with innumerable setbacks increased his numbers until by 1650 he attained the respectable figure of over 500 million persons, of whom 100 million were Europeans. Then, at an accelerating

\* Read April 12, 1939, The New York Academy of Medicine.

rate, births exceeded deaths, until in the early nineteen hundreds the increase of the white race reached its peak, a rate of increase of 40 per cent per generation (about 12.8 per 1000 per year). By 1933, Europeans and their descendants numbered 700 million,\* a sevenfold increase in ten generations, while the human race as a whole had increased almost four times to something over 2 billion.

In the United States, the ten years, 1920-1930, marked the greatest addition to our numbers of any decade in American history, over 17 million people. Yet, coincident with this unexampled proliferation of the human species, there were unnoticed forces working towards a reversal of these trends. For a hundred years births per married women had been on the decline. After 1900, this decline became more rapid, but was hidden for a time by a remarkable decline in deaths, the excess of births above deaths remaining high. Thus, by 1932, while the crude birth rate had dropped to 17.4 per thousand, the crude death rate was only 10.9 per thousand, leaving a crude rate of natural increase of 6.5 per thousand per year. But in the same year, 1932, for the first time in our history, the women of childbearing age in the United States were failing to have enough children to replace their own number in the next generation.

#### CRUDE VERSUS INTRINSIC RATES OF INCREASE

In order to understand this paradox, it is necessary to have a clear picture of the difference between "crude" rates, as ordinarily reported, and "true" or "intrinsic" rates as used by students of population. Crude rates are rates of births or deaths per thousand of the population. The difference between these births and deaths is the crude rate of natural increase. Thus, if the crude birth rate is 17 per thousand of population per year, and the crude death rate is 11 per thousand of population per year, the crude rate of increase is the difference between the two, or 6 per thousand of population per year. These were approximately the rates for the United States in 1935. From these rates it would appear that the population is increasing rapidly. But if only 11 people out of every thousand died each year in a population with stabilized age distribution, the average length of life would be about 90 years, which is quite contrary to the known facts, the average span of life for our total population (White and Negro) being about 61 years. The crude death rate of 11 per thousand is so low because the present population of the United States,

\* Estimate by Beloch as revised by Caviagnac.<sup>1</sup>

as a result of changing rates of fertility and mortality and immigration contains an unusually high proportion of people in the middle age groups where death is least frequent. When the passage of time has corrected this proportion we can hardly expect a crude death rate of less than 15 per thousand, which would be appropriate to an expectation of life of sixty-six years, five years more than our present average.

Birth rates also are affected by the present high proportion of young adults in the childbearing ages, there are naturally more children born each year per thousand of population when the proportion of young adults is high, than would be the case if the proportion of non-childbearing old people were larger. Crude rates of reproduction are, therefore, a poor index of future trends.

Evidently we want to know whether the women of childbearing age are at any given time having enough children to replace their own number in the next generation. Statisticians can figure out the answer provided they have available vital statistics which show for any given year the number of children born to women in each age group during the childbearing period, and the death rates for each age, from birth to death.

From these specific rates are obtained gross and net reproduction ratios and, after taking into account the average interval between births in two successive generations, intrinsic rates of natural increase.

These new methods of ascertaining intrinsic rates of reproduction make it possible to forecast quite accurately the changes which will take place in a population for a generation ahead, if we omit consideration of immigration. The children born today will, subject to prevailing mortality rates, be the parents of the children born 30 years hence, just as they will also be the candidates for Townsend benefits about the year 2005. Thus short-term forecasts covering not more than a generation can be made with considerable accuracy. Estimates over a longer term depend chiefly on the assumptions made about future birth rates. Death rates are less important to such estimates. At the time of the 1st census, 89 per cent of the white females born alive lived to the center of the reproductive period<sup>2</sup> a loss of only 11 per cent due to mortality. Thus today births and not deaths are the primary factor in selection for survival.

### THE DECLINE IN BIRTHS

The population study of the National Resources Committee in 1938 presents estimates by Thompson and Whelpton of the future growth

of this country on three different assumptions of low, medium, and high fertility. On the assumption of low fertility, with no immigration, the maximum population would be 140 million, reached in 1960. On the assumption of medium fertility, the maximum would be 153 million reached in 1980.

For the past several years every new estimate has shortened the time remaining before the peak of population will have been reached and the decline in gross numbers will commence to set in. At present the intrinsic rate of reproduction is about .95, five per cent short of the rate required for replacement. This rate would be even lower if it were not for the high birth rate in the rural sections of the country. But the high rate in rural states is falling, and there is no sign of an increase in the urban states which are already far below the replacement level.

In much of Europe the decline in births began earlier and has gone farther. England had a net rate of reproduction of .76 in 1936, 24 per cent short of replacement, France, a net rate of .87 in 1935, Germany a net rate of .88 in 1935, after having been as low as .70 in 1933, Sweden a net rate of .70 in 1934.<sup>3</sup>

In the United States the decline in births is closely related to a growing urbanization. Cities of over 100,000 have a net rate of .75, twenty-five per cent short of the rate required for replacement. Cities down to 25,000 of population, and towns of 25,000 to 10,000 people, show rates of .88 and .97 respectively, just short of replacement. The small town breaks even with a rate of 1.04. Only the rural village, with a rate of 1.37, and the rural farm, with a rate of 1.69, are making substantial contributions to an increase of population. Because farmers in the South are so numerous and so prolific, their children will largely inherit what remains of the urban civilization we are trying to build.

Variations in birth rates with size of community result in interesting racial variations in reproduction. The Jews, who are concentrated in metropolitan centers, with high educational standards, are probably fifty per cent short of having enough children to replace their number in the next generation. Anglo-Saxons, because they are so numerous in the isolated, rural sections of the South, are more than holding their own. Negroes, about equally balanced between city and country, show the same rate of reproduction as does the country as a whole. Mexicans and Indians, the most isolated of all our peoples, are almost doubling their number in each generation.

## DECLINE IN THE PROPORTION OF LARGE FAMILIES

Wide differences in net rates of reproduction are very largely due to differences in the proportion of large families. In California, with the lowest rate of reproduction of any State in the Union, only 10.1 per cent of the families of fertile married women consisted of five or more children even prior to 1928.<sup>4</sup> In North Carolina, a State near the top of the reproductive list, 32.4 per cent of the fertile married women had five children or more, three times the proportion prevailing in California. And in English marriages of 1860 and 1870, one-half of the women had five children or more, with an average of eight children.

To maintain our present population would require something over 2.6 children per married woman. Taking into consideration the number of sterile marriages, we find that fertile couples must have on an average over three children to provide population replacement. But since not all fertile couples will have three children, some must have four and some five children to bring the average up to three. Almost any way we figure, we find that approximately 20 per cent of married women must have five or more children if the reproduction of the population is to be at a rate sufficient for replacement. And under the conditions of life in our cities and towns, nothing like 20 per cent of married women actually have families of five or more children. Among most professional groups, such large families are looked on askance.

In seventy years the proportion of these large families in our cities has fallen from 50 per cent to about 10 per cent. Is this due to a physiological inability to bear many children, brought about by the strain of modern life, or is it the result of a deliberate restriction of size of family? All available evidence points to the conclusion that voluntary control of family size has been the principal factor in the decline in births. Recent studies by Pearl<sup>5</sup> offer almost overwhelming proof to this effect. Among 30,000 women studied in hospitals in the eastern part of the United States, women practicing family limitation most intelligently and consistently had pregnancy rates from 50 to 75 per cent below those who reported no such efforts whatever. Among the women who reported no attempts to limit their families since marriage there appeared to be no significant difference in pregnancy rates whatever their economic status or the size of community in which they lived. To quote Pearl's conclusions: 'In the population of the United States at least the fertility

differentials relative to race (Negro versus White) and to the three most important social class differentiations (economic, educational, and religious) are due primarily to differences in the relative prevalence and effectiveness of the efforts made to prevent conception, correlatively aided by relative frequency and postponement of marriage and the practice of criminal abortion, and to practically nothing else ”

The use of birth control and the deliberate effort to restrict size of family is only a manifestation of underlying attitudes and customs. The decline in births is the result of numerous and complex causes. Any considerable increase in reproduction will probably depend on quite profound changes in economic and social relationships and on changes in personal values and attitudes toward family life.

This brief analysis has interesting implications for the medical profession. At present this country is well populated and thoughtful people would look on a reasonable decline in numbers with equanimity. But it is almost certain that with the extension of birth control services, an extension which seems inevitable and is almost certainly desirable, our net rate of reproduction will fall to 70 or less. At a level 30 per cent or more below the rate needed for replacement—and that is the direction we are headed for in the country as a whole—and a much lower rate for people at the high school level, there will be strong social reasons for bringing up the rate of reproduction at least to the replacement level among the more competent people who make use of the doctor's services. Doctors will feel the pressure of the demand for an increase in births and they will find that such an increase will depend very little on the science of medicine as it may effect a decrease in sterility, but very largely on the personal relations of the physician with each individual family through which he may influence their attitudes and their desire for children. And among a substantial proportion of couples the desire for children must extend beyond the one or two children who are supposed to satisfy the maternal instinct of modern women. Without numerous families of four or more children, reproduction will never approach the replacement rate.

#### NATURAL SELECTION IS STILL EFFECTIVE

If the decline in births is the result of cultural factors under man's control, it is equally true that the accompanying decline in deaths is the

result of consciously directed efforts, particularly those of the medical profession. Some biologists have claimed that these artificial and man-made conditions have limited the force of natural selection and increased the reproduction of the weak and unfit. The evidence on this point is far from conclusive. Expectation of life at birth has increased from 49.2 years in 1900-1902 to 60.3 in 1929-1931. About four-fifths of this saving is due to the decrease of deaths between birth and the center of the reproductive period. The proportion of infants who live to reproduce is therefore much greater today than it was even a few decades ago. The predominant factor in this change has of course been the control of infectious diseases. In 1901, 12.4 per cent of all infants died in the first year of life, as compared to 5.8 per cent by 1930, a reduction of one-half in the death rate in thirty years. But during this period, deaths in the first month were reduced by only a fraction, from 4.1 per cent in 1901 to 3.1 per cent in 1930, while deaths in the next eleven months declined from 8.3 per cent in 1901 to 2.7 per cent in 1930.

The reduction in deaths after the first months certainly appears to be due chiefly to improvements in feeding and medical care, with relatively small relation to variations in known hereditary qualities. But deaths in the first month would appear more largely due to either parental or hereditary causes. The fact that births in the first month show a relatively small decline, seems to indicate that natural selection is still operating. In view of the recent extension of medical and public health measures it is probable that improper care of expectant mothers and accidents of birth will play a still smaller part than in the past in causing the death of newborn infants, and that hereditary conditions will be even more important than previously.

Not only has there been little progress in reducing deaths among newborn infants but equal difficulties have been found in combating the diseases of old age. In the organic and degenerative diseases of old age hereditary factors are also known to play a large role. We would expect this to be the case. These diseases rarely affect people until they have completed their reproductive period, so that the force of natural selection has not had a chance to eliminate such strains. But here too previous infections and improper conditions of life are responsible for a vast amount of preventable suffering and untimely death.

Medical science does undoubtedly in some cases save the lives of individuals with serious hereditary handicaps. In so far as the persons



saved may later have children themselves, there may result an accumulation of genetic factors that will cause greater hazards, costs and suffering for future generations. It is desirable therefore that progress in medicine be accompanied by progress in human genetics and social science, making possible the isolation of specific pathological factors, an understanding of hereditary mechanisms, and a humane program designed with reference both to the immediate physical and psychological needs of affected individuals and the more ultimate objectives of public health. Natural selection is still the major force for eliminating extreme deviations. But in proportion as it is the proper business of physicians to oppose untimely deaths as a factor in natural selection, so it is the physician's responsibility to use all his influence to limit conception among those who may be properly suspected as being carriers of serious hereditary defect. This is a new function for the doctor and one he is reluctant to assume. But it flows inevitably from the doctor's new control over death, and from man's increasing power to regulate births, and there is no one but the physician whom the public will or should trust for advice on so vital and personal a matter. If this new function is to be properly discharged, there must be a great increase in research in human genetics, and the results of such research must be rapidly assimilated by the medical profession.

#### MENTAL DISEASES

Fortunately, the death rates of persons suffering from mental disease are far higher than those for persons of similar age in the general population. Even with modern institutional care and in the case of mental diseases that do not involve any known physical disorders, the death rates of the insane are extremely high. This is shown by a comparison of standardized death rates for mental patients and total population in New York State.

A comprehensive investigation of factors affecting the net reproduction of the mentally diseased has recently been published by a Swedish scholar, using data on schizophrenia (*dementia praecox*), manic-depressive psychosis, and epilepsy, drawn from the archives of the Kaiser-Wilhelm-Institut in Munich,<sup>6</sup> and compared with appropriate samples of Munich and rural Bavarian population.

The results of this investigation show that the net reproduction of schizophrenics and epileptics is distinctly less than that of the general

population in the same area and at the same time. This is due in part to high mortality after mental breakdown, but in still greater measure to the low marriage rates characteristic of the psychotic—both before and after the onset of mental disorders. The reduction of net reproduction rates due to these factors is negligible in the manic-depressive group, because of the late onset of manic-depressive disturbances.

Landis and Page, in their book, "Modern Society and Mental Disease," written in 1938, have carefully analyzed admission rates to mental hospitals and come to the conclusion that there is not any marked increase in mental disease either in the United States or in England, Belgium, Norway or France.

While natural processes thus appear to set limits to the reproduction of these defective stocks, the present number of the mentally sick is so great as to constitute the greatest single source of hospital expense and human suffering in this country today. But there is worse to come. Dr. Harold Dorn of the U. S. Public Health Service has recently shown that there will soon be a doubling of mental disease, assuming present rates for different ages, solely because of the increasing proportion of older people.

There is considerable evidence to indicate that hereditary factors affect susceptibility to many types of mental illness. Additional research is badly needed, but there are already strong grounds for discouraging the present practice of some psychiatrists of advising women patients that childbearing may improve their health. Such advice seems not only undesirable in the light of the genetic probabilities, but also because highly neurotic parents do not usually provide the optimum of home environment for the rearing of children. Here again, there is indicated an urgent need for research in medical genetics to determine more exactly the extent to which mental diseases may be related to hereditary factors and to develop methods by which medicine can supplement the already favorable trends of natural selection toward the further reduction of this prevalent and expensive form of disease.

#### CHANGES IN AGE COMPOSITION

Present population trends make for rapid change in the proportion of persons in the different age groups. Estimates by Thompson and Whelpton indicate the following changes over a period of 100 years:

It is in the group of 65 years and over that the most striking change

TABLE  
A CENTURY OF POPULATION TRENDS IN  
THE UNITED STATES, BY AGE GROUPS

<i>Age</i>	<i>1880</i>	<i>1930</i>	<i>1980*</i>
Under 5	13.8	9.3	6.4
5-19	34.3	29.5	20.3
20-44	35.9	38.3	35.4
46-64	12.6	17.5	25.8
65 and over	3.4	5.4	12.1
Total	100.0	100.0	100.0

has been going on and will no doubt continue. While the proportion over 65 years of age may more than double in the next fifty years (5.4 per cent in 1930, 12.1 per cent in 1980), the change in absolute numbers is even more startling. These elders were over tenfold as numerous in the population of 1930 as in that of 1850, and may increase threefold over the present by 1980.<sup>8</sup>

In considerable part these changes in the proportion of persons at different ages result from the work of the medical profession, for it is not only the decline in births but also the conquest of infectious diseases which is piling up the number of those in the older groups. Thus, the solution of some of the most vital medical problems of infancy and youth has intensified a new set of problems, those connected with old age. Here new methods of attack are required. In the diseases of old age, changes in the patient's way of life may be necessary over long periods, the physician's care must be more continuous and personal, requiring more knowledge of traits of personality and family background. Hope for a rapid cure gives place to the desire to alleviate suffering and to extend the serviceable years of a mechanism beginning to wear out. In some ways these factors may seem to indicate an increasing need for the family physician rather than the specialist. On the other hand, early diagnosis is at a premium, together with a new emphasis on constitutional and genetic relationships, and here the advice of specialists would be important. Again, there is indicated the need for research in human genetics.

#### DIFFERENTIAL FERTILITY

To those engaged in the study of population, today's trends in births present a vivid picture of birth differentials. Persons living on the farm

\* Estimated by Thompson and Whelpton.

are, on the average, producing 50 per cent more children than the number needed for their replacement in the next generation, those in the great cities are 25 per cent short of enough births for replacement. The isolated and impoverished rural sections reproduce at an even higher rate—over large areas at 200 per cent of the rate required for replacement—while the more educated persons in the cities, say, at the upper high school level, are having only half of their replacement quota. For broad occupational groups the differences, while less extreme, are still striking, as shown by the following data from the U S Registration Area in 1928,<sup>4</sup> the replacement figure being taken at 100

Professional	76
Business and Clerical	85
Skilled labor	106
Unskilled	117
Agricultural labor	132

Throughout the entire United States, with few exceptions, reproduction is highest among those most isolated, most limited in economic opportunities, most lacking in educational facilities.

Apparently differentials between occupational groups have been increasing since the middle of the 19th century, chiefly because of voluntary control of births, but also because medicine and sanitation have reduced differential death rates which formerly offset in part the reproductive effect of differential birth rates. In England and Wales, Notestein<sup>9</sup> finds that just prior to 1860 upper- and middle-class rates of reproduction were about 10 per cent below the rates for the country as a whole, and agricultural workers, who then—as now—headed the list were less than 10 per cent above the nationwide average in reproduction; whereas, by the end of the century agricultural workers were almost 30 per cent above the average and the upper middle-class group almost 30 per cent below the average. Recently, there has been some evidence that these differentials have reached their furthest spread and are beginning to come together again. In the top income groups with the greatest economic security, there is a tendency to have somewhat larger families than those found among the next lower income ranks. In many European cities, the usual class differentials have been to some extent reversed in recent years. Those persons at the very bottom of the scale still have the most children, but from skilled workers up there is a slight increase as one goes to business executives and the professional classes. But

this reversal has been brought about not by any increase in births at the upper levels, but by a decline in births in families at the lower occupational levels, so that reproduction as a whole is at a very low level. In Stockholm, for instance, the women of childbearing age are having only one-third of the number of children necessary for replacement. In this country the low record seems to be held by Portland, Oregon, with a rate of 50 per cent of replacement.

It seems likely that the trend in this country will be towards gradually smaller differentials between occupational groups. Such a trend is highly desirable for many reasons. At present a major part of the country's children are being born and reared in those American homes least able to provide adequate nutrition, adequate physical care or a stimulating educational environment. Thus in a real sense the work of public health and educational agencies has to be done all over again in every generation. Such a situation must go far to offset the great efforts now being made to raise the general level of public health and education. Those who are interested in improving the conditions of human life will want to hasten the natural trend towards a greater equalization of births.

The most obvious means of bringing about an equalization of births is to increase the availability of birth control and extend its use to all couples desiring to limit the size of their families, regardless of their economic situation or isolation. Quite apart from its other aspects, more effective use of contraceptives is probably the only practical alternative to abortion among many persons desiring to limit the size of their families. The medical profession can hardly escape its responsibility for directing the proper use of new methods of control over conception. Undoubtedly birth control will continue to be extended to persons to whom it is not now available, and as this process continues, there will be a further decline in the general level of births.

Under present conditions of American life, birth control alone would effect an equalization of births at a level of reproduction probably about half that needed for replacement. Such a low rate would be a denial of the nation's future. A permanent redistribution of births must be based not on birth control alone, but on birth control in combination with agencies which will increase births among competent parents who are able to give their children a decent physical, moral and mental environment, whatever social or occupational class they may belong to. Such an increase in size of family among competent people is essential not only to

offset the decline in births due to the increased use of contraception, but also to make the force of good home environments effective among a large proportion of the country's children. And there are a priori grounds for believing that an increase in size of family among competent people in all ranks of society is also essential for maintaining the genetic level of American stocks.

#### FORCES AFFECTING SIZE OF FAMILY AMONG COMPETENT PEOPLE

Measures designed to increase births among competent people will be necessary to offset the further decline due to the extension of birth control. Such measures will undoubtedly include economic changes which will reduce the cost of having and rearing children. More free prenatal care, reduced maternity costs, and free health services for young children, seem almost certain items in the Nation's budget in the near future. But these and other measures for reducing the cost of children will not themselves lead people to have larger families. They are a preliminary to those changes in attitudes towards family life and children which can only be brought about by new types of impacts in the social and emotional environment. It will be no easy task to increase the desire for children among thoughtful people in our urbanized mechanical civilization. Every type of social agency will have to take part in such an effort. The greatest changes will perhaps be required in educational institutions which, until now, have given little thought to the effect of education on the development of the emotional life of the individual. But the most direct influences will be those effected in personal contacts. It is difficult to imagine any effective change in people's attitude toward having children without including doctors in the list of those taking an intelligent part in attempting such a change.

It is to the doctor that a woman first confides her hope that she is to become a mother. Does the doctor report the results of his examination with a laconic statement that she is in trouble, or does he strengthen her with the realization that this is the normal fulfillment of her feminine role, to the probable improvement of her health, and to her future happiness? If she has already several children, is his attitude one of admiration or of commiseration? Shortly she must decide whether her confinement is to take place in a hospital or in her home, and again she turns to her doctor. Is the doctor's advice weighted by consideration of where she will have the greatest comfort and pleasure in her baby, so that she may

look back on the first few weeks after the baby's arrival as a period of infinite happiness and charm? Will the nursing care and the environment during convalescence provide a favorable atmosphere? Students of population increasingly suspect that the attitude of the father often determines ultimate size of family. Does the doctor have this in mind, and do everything possible to bring the father into an intimate relation with the thrilling and beautiful aspects of bringing a new life into the world? Or is the father excluded at the start, and thus brought to think of this only as a period of anxiety and painful separation?

In the first week or so of the baby's life, the mother must decide whether she will try to nurse it herself or have it fed on a bottle. In advising her what she should do, does the doctor take into account those subtle emotional needs to which modern psychologists give such weight? The need of the mother for the full development of that relationship with her child, which may be weakened at its inception if she does not hold it in her own arms and feed it from her own breast. The need on the part of the baby for that warmth of security, that fullness of satisfaction, for lack of which its own emotional life may be in some degree stunted.

After the baby is weaned, family contacts with the doctor still continue. His attitude, and even sometimes his direct advice to both parents, will inevitably influence their decisions as to whether they should have additional children. Will the doctor in every case study these conditions, over and beyond the state of the mother's health, which affect the social desirability of their having more children, the home environment in which they will be brought up, the probability of their having a sound heredity?

These may seem strange questions to put to the members of the medical profession, pressed as they are by their present duties. But they do not seem strange questions to the student of population. The sterility of those who are most affected by modern civilization in this country and abroad is not in the main a physiological sterility. It is an emotional sterility, of which birth control is only the tool. We have created an environment in which the bearing and rearing of children is economically difficult, and concurrently we have both lessened the force of those influences in the environment which make for normal emotional development, and enormously increased the influences which make for the development of attitudes and values incompatible with the desire for children. That is

the picture as it appears to students of population in this country in recent years

The medical profession by sanitation and the control of infectious disease has brought about an extraordinary decline in deaths. This decline in deaths has been accompanied by an extraordinary but highly unequal decline in births. A favorable distribution of births at present levels of reproduction would help stabilize recent advances in civilization and strengthen all efforts at further improvement. The question whether a favorable distribution of births can be aimed at a level sufficient for replacement presents one of the major problems of our present form of society. A clear understanding of this problem by the medical profession may be one of the deciding influences in its solution.

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## IRRADIATION IN THE LYMPHOMATOID DISEASES\*

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THE TERM lymphomatoid diseases embraces an extremely complex collection of morbid and mostly lethal processes. It is outside of the scope of this paper to discuss the few facts and the many theories concerning their causes, or to portray the wide scope of the pathologic changes which they may produce. There is no part of the human body entirely exempt from the possibility of being affected directly or indirectly by these diseases, and there is no age entirely immune from them. They concern therefore, every practitioner of medicine.

Even within the scope of any one of the so-called entities, such as Hodgkin's disease, variations are so great that each case becomes an individual problem for treatment. Yet they do have one thing in common in connection with treatment, and that is that irradiation by Roentgen rays or radium continues to be the single most effective method.

These diseases were among the first to be treated by irradiation, and even with the earliest crude techniques showed some remarkable responses. Yet they are so variable and unpredictable that their treatment by irradiation has remained an art rather than a science, to a degree greater than is true for many of the malignant tumors. In the treatment of some types of cancer, radiation is becoming one of the tools of the surgeon, used much as he might apply the knife or cautery. In malignant tumors affecting restricted parts of the body, for example epitheliomas of the lip, tongue, hypopharynx, skin and cervix, the radiant energy of radium and x-rays may be applied in a highly accurate manner, with rigid specifications of portal shape and size, direction of beam, amount and frequency of dose. Thus, the new type of specialist, the surgeon-radiologist, can develop a fairly standard technique, often combining a surgical procedure with a routine of irradiation that for a given type of cancer may be allowed to remain fairly fixed for a time long enough to permit

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judgment of results

In the group of lymphomatoid diseases on the other hand, because of their great variations, it is hardly possible to devise a general routine, except perhaps for some of the commoner forms of local lesions, such as tonsillar lymphosarcoma, or Hodgkin's disease restricted to one or two groups of nodes. Yet the problem of determining the optimum technique of irradiation for these local lymphomatoid lesions is difficult. The ease with which regressions are secured by small doses may lead to a false sense of accomplishment, where much larger doses would be needed to effect actual sterilization of the disease. On the other hand, with large doses one may use up the patient's tolerance of radiation in producing regression of one lesion, only to find that other foci soon appear, and then the patient is less well able to withstand further irradiation.

Since we cannot hope to discuss all the possible variations of these diseases and consequent modifications of treatment even solely from the aspect of irradiation, let us therefore take up one by one the commoner types and indicate certain general plans of treatment. We must in advance recognize that cases must be individualized and that a given case may not fit neatly into these plans. We must also recognize that techniques of different workers vary considerably, that in these diseases, which are usually rather radiosensitive, widely different techniques may seem to give about equally good results, and that judgment about the value of a given technique is most difficult in such variable disease processes.

What I shall do here is to outline roughly our current preferences in modes of irradiation, with no claim that these methods are the best. There is no time here to discuss differential diagnosis, so we must assume in general that the diagnosis has been established, by biopsy if possible, and this we are doing routinely.

At this point we may consider briefly the types of radiation suitable for the treatment of these diseases. Beginning with Roentgen rays we have

1. Low voltage Roentgen rays generated at or about 100,000 volts suitable only for superficial lesions. These may be used unfiltered for very superficial lesions or up to 4 or 5 millimeters of aluminum filter may be employed in order to screen out the longer less penetrating wave-lengths and thus give a type of radiation suitable for lesions of some thickness on, in or close under the skin.

2 Intermediate voltage Roentgen rays, generated at 140,000 to 160,000 volts, filtered by 3 to 6 millimeters of aluminium. Some workers prefer this type of irradiation even for deep seated lesions—rather illogically, I think, because there is too much effect on the skin and overlying tissues in proportion to what reaches deep parts.

3 High voltage Roentgen rays, usually generated at about 200,000 volts and filtered by 0.5 millimeters of copper or its equivalent. This gives adequate penetration to reach deep parts, and by increasing the target skin distance up to 70 or 100 centimeters or more a quite satisfactory depth dose is obtained without undue effect on the skin.

4 Super-high voltage Roentgen rays generated at 700,000 to 1,000,000 volts or more are probably entirely superfluous in the treatment of the lymphomatous diseases.

When low voltage and high voltage Roentgen apparatus is available, I see no great necessity for radium in the treatment of these diseases, except that extremely rarely there may be an indication for interstitial implantation of radon seeds or needles. Anything that can be done in this field by external application of the gamma rays of radium apparently may be done just as effectively and often more conveniently by Roentgen rays. We do at times use the 4 gram radium pack for external irradiation in place of the high voltage x-rays but not as a rule by preference.

### HODGKIN'S DISEASE

Given a case with an established diagnosis of Hodgkin's disease, two questions must be answered as well as possible before planning treatment. First, how extensive is the disease? Second, how acute a process does it seem to be? These questions can only be answered by a careful survey of the case, including history, physical examination, and roentgenographic studies. If, in a patient with very slight or no constitutional symptoms the disease seems to be limited to one group of nodes, as in the neck, one is probably justified in irradiating that area heavily in the hope of complete sterilization. At present we might give such a field 200 r daily or every other day to a total of 2000 r or more. Yet a word of caution at this point: experience in observing large numbers of cases of this disease suggests strongly that such a group of external nodes, apparently the only focus of the disease, is actually only an external sign of a process that gained entry to the body somewhere within the drain-

age territory of those nodes, and that therefore we must be on our guard against the possibility that the disease is already present elsewhere. Especially suspect are cases with a group of nodes at the base of the neck, in the axilla, or in the groin. Such cases call for careful examination of the chest and abdomen. When no internal focus can be found to account for the spread of disease to such an external group of nodes it may well be assumed nevertheless that the *noxa* of the disease, whatever its nature may be, has gained entry into the body at the appropriate internal site and has passed on, probably, however, leaving minimal undetectable traces internally. Therefore, in such situations the question always arises whether one should not give some treatment to the appropriate internal sites. For example, with a group of nodes situated at the base of the neck, in the position of the node of Virchow, even the absence of demonstrable disease in mediastinal or retroperitoneal territory would not exclude from our minds the advisability of giving some treatment to those regions. We do so in many cases but, because of the absence of demonstrable disease in those fields, we tend to give considerably smaller doses than we do to the known focus. We hope that the internal foci may actually be minimal and that smaller doses will serve at least to hold the process in check. We fear that larger doses might too greatly depress the patient's reserves and thus prevent us from giving full treatment if some other definite focus does appear.

To go back for a moment to the treatment of the mass of external nodes, I am by no means certain that the divided dose method of say 200 r every other day to a total of 2000 r is preferable. The dose of 200 r is about the upper limit of a single dose in the hands of most workers. However, some years ago we were giving such cases single doses of 400 to 600 r repeated at varying intervals for a few times. Some of the longest survivors we have had were treated by these fewer but larger doses, and therefore at the Fifth International Congress of Radiology in Chicago last year I ventured to raise the question whether such a method might not be preferable at least in some cases.

Many cases of Hodgkin's disease when first seen present more than one area requiring treatment but are not yet in an advanced stage. In these cases each field is usually treated by 200 to 300 r every second or third day to a total of 1000 to 1200 r a field. Usually good regression will promptly follow such treatment.

Even cases that are far advanced may be greatly helped by judicious

irradiation If severely anemic, such patients may be temporarily strengthened by transfusions so that they will better withstand treatment and obtain more good from it When there are many areas of disease we usually do not try to treat all of them in one course, but select the larger and more important foci, giving them doses chosen empirically according to the bulk and depth of the lesions, and according to the condition of the patient Some areas may receive 200 to 300 r two to five times at daily to weekly intervals, others about 400 r once Then we may wait for three or four weeks, to give the patient a chance to get the benefit of this partial treatment If we have been intelligent in our choice of areas and dosage, improvement may far exceed expectations, and then we have a patient better able to go on with further treatment Literally, at times, patients with far advanced Hodgkin's disease seem to be pulled back from the brink of the grave by such measures, though at times our choice is not correct, or the disease is even worse than we thought, and we fail

In some cases with widespread disease it may be well to include large fields such as the entire mediastinum, or the entire central abdomen or even greater sections of the trunk in single beams of radiation used at long target skin distances Rather routine irradiation of large body fields is advocated particularly by Sluys of Belgium, Gilbert of Switzerland and Desjardins of the Mayo Clinic I prefer to avoid routines and to choose areas according to the indications of the particular case

Instead of irradiating the body in huge sections one may arrange the apparatus so that all or nearly all of the body may be irradiated at one time either in short individual sittings as is done in Europe and in a few centers in America, or at low intensity and continuously for days as we have done at Memorial Hospital in the unit named for Doctor Heublein, who suggested the latter method In Hodgkin's disease irradiation of the entire body is used at Memorial Hospital only in small doses in selected cases and as a supplement to local irradiation One cannot expect the body to tolerate enough exposure to radiation distributed simultaneously over its whole surface to produce satisfactory regression of bulky masses of granulomatous tissue Yet, when the local masses and infiltrations have been treated we find in selected cases that by supplementing their treatment by small doses of general body irradiation, one gains frequently a tonic effect, with increase of weight and sense of well being, and freedom from recurrence of signs of disease activity for periods longer

than would otherwise be expected. We must freely admit that this statement is based on observation of numbers of cases, and that it is hardly possible to prove it by statistics. Even if some years from now unusually good survival figures appear among cases treated by general irradiation, one would have to take into consideration also the belief that the methods of local irradiation in the same cases had probably been more efficient. It has not seemed fair to restrict the treatment of any of these patients to general irradiation to see what it alone could do. Whether using general or local irradiation due regard must be had for the patient's tolerance, as judged both by his general state and by his blood count. If the white cell count becomes too low, say about 3000, it is usually best to suspend treatment for a time. However, it is important to point out that in some cases, in which no radiation has been used, a leukopenia will be found. As a rule one may proceed with irradiation in such cases, for it is probable that the low white cell count is caused by the disease, and that irradiation may actually be followed by a rise of the count to normal.

#### HILAR TUBERCULOSIS AND HODGKIN'S DISEASE

In recent years several cases have presented themselves in which it has been very difficult to make a differential diagnosis between hilar tuberculosis and Hodgkin's disease or possibly lymphosarcoma. These are cases in which the Roentgen film shows distinct enlargement of hilar and tracheobronchial nodes of a pattern like that seen in the childhood type of tuberculosis, and in which no enlarged external nodes are available for biopsy. In such cases a negative tuberculin test is regarded as strongly suggestive that the process may be Hodgkin's disease, and accordingly that it may be safe to proceed with irradiation of the mediastinum and hilar nodes. It seems best to begin treatment cautiously however, in order to test the response.

If, after a month or two a slight regression can be found and if there has been no unfavorable reaction it is considered safe to proceed with intensive irradiation, as for Hodgkin's disease.

As for results we find 17 per cent of patients with histologically verified Hodgkin's disease surviving for five years or longer after treatment was begun. Certain workers report considerably higher five year survival figures than these. I feel that in such series there must have been a selection of cases accepted for treatment. Our figures apply to all cases coming to us in which the diagnosis was proved microscopically.

We reject only moribund patients and those who are under treatment elsewhere and come without permission of the physicians who are treating them. At one time recently we counted twenty-two patients living over five years, and we have now one patient who has survived over seventeen years. She was seemingly free of disease for about fifteen years but developed a mediastinal recurrence a few months ago. This was treated with fairly good response and she is still in good condition.

The most important factor of all in the treatment of Hodgkin's disease, or any of the lymphomatous diseases, is close vigilance for earliest signs of new foci or recurrences. Increased attention to the possibility of lesions of the lungs, bones, deep lymph node areas, nerve roots, spinal canal, and other tissues, leads to earlier detection, or to justified assumption of need for treatment of these parts, and thus to improved palliative results. Increased attention to such supportive measures as transfusions, iron, vitamins, and a general regime as for tuberculosis rewards us with better responses to irradiation and prolonged, more comfortable survival of our patients.

### LYMPHOSARCOMA

If in a case of lymphosarcoma the disease is apparently localized in one field, aggressive irradiation is justified in an attempt to cure. Usually such attempts fail, but there is a fair percentage of salvage among such cases, for long periods, if not actual cures. Yet here again we are dealing with variable, unpredictable processes and cases that seem bad may do well, while those that delight us by early complete regression may soon dismay us by the rapidity with which their disease returns and spreads.

In younger individuals, cases beginning as lymphosarcoma, sometimes apparently atypical and seemingly hardly more than an inflammatory process, regressing remarkably well under irradiation, may then rapidly develop a full blown picture of acute leukemia.

In cases of localized lymphosarcoma in which there appears to be a chance to secure complete sterilization, I feel that it may be a mistake to limit the size of the port to an area just large enough to include the palpable tumor, and to protract the treatment by giving small fractional doses daily. In this very cellular disease, tending to infiltrate widely, I believe it preferable to use ample ports and to give larger doses at a time. This is in contrast to the generally used procedure of small doses of low intensity repeated twice a day, daily or every other day to the same

port until a large total dose is attained — sometimes an epidermicidal dose. Some advocate large ports, others would treat lymphosarcoma as they do epidermoid carcinoma by ports kept as small as possible so as to include only the demonstrable part of disease. This is following the principle of treating cancer only where you find it, a principle which needs modification when we deal with lymphosarcoma. Yet we are finding that reticulum cell lymphosarcoma is not always nearly as radiosensitive as was once believed. When we find a case of localized lymphosarcoma that is relatively radioresistant it is probably better to use the protracted divided dose method, as in carcinoma, so that a much larger total dose can be given. In such a case I feel it would be advisable to restrict ports as much as possible for two purposes, first, to spare the patient the effects of as much irradiation of extraneous tissue as possible, and, second, to permit an increase of the dose to the tumor.

When a patient with lymphosarcoma has several widely scattered areas of the disease, obviously one must plan for the best palliation, rather than an attempt to cure. It then becomes a matter of proper choice of areas to be treated first, of individual and total dosage and the intervals between doses. In cases with widespread lymphosarcoma the use of the larger individual doses permits a more rapid coverage of most of the disease, while the protracted small dose method would necessitate a hopelessly long program. Just in this type of case in which the advocates of rigid adherence to that rule of treating cancer where you find it, using small ports and protracted dose methods, would tend to give up and say that such a case is better not treated at all, may be found some of the most worth while results of irradiation in palliation.

#### RESULTS IN LYMPHOSARCOMA

Of 132 patients treated, 1918 to 1933, inclusive, in whom results can be determined, there were twenty-one or 15.9 per cent, who survived five years or longer. Five of these died after five years, while two are living over five years with evidence of disease so that there are fourteen, or 10.6 per cent who survived five years or longer and who had been free of evidence of disease for six months, and in many cases much longer ever since the regression that followed the first course of treatment.

#### MYCOSIS FUNGOIDES

The superficial tumors and plaques of infiltration of the skin in this



disease are usually very radiosensitive in the beginning, and may yield readily to relatively small doses of low voltage x-rays. However, in many cases there is such widespread involvement of the skin that adequate treatment of all the disease would require more radiation than the patient could tolerate, so that each course of treatment must be restricted to the lesions that are most troublesome or threatening at the time. In later stages the recurrences that may appear in previously irradiated fields may be rather resistant, and lesions may appear in lymph nodes, bones, lungs and other viscera, requiring palliative treatment as for like lesions of advanced Hodgkin's disease or lymphosarcoma.

### THE LEUKEMIAS

In the treatment of leukemia by irradiation it is quite important to gauge the degree of acuteness or chronicity of the process clinically as well as hematologically. No sharp line of demarcation exists between acute and chronic forms but the more acute cases must be irradiated, if at all, with great caution. Even the more chronic cases may be greatly harmed by overenthusiastic treatment. Undoubtedly some leukemics have been killed by radiation effects. Yet judiciously applied radiation can be of benefit even in some cases apparently very acutely ill, and seemingly almost moribund.

It is especially in chronic myelocytic and chronic lymphocytic leukemia that irradiation plays a great part in bringing about restoration of the patient, for periods of varying length, to comparative or apparently complete health and economic usefulness. While statistics seem to show not more than a few months, possibly, of prolongation of life on the average, as compared with untreated cases, yet it seems evident that in some cases the inevitably fatal termination is considerably postponed by irradiation.

### CHRONIC LYMPHOCYTIC LEUKEMIA

The typical case of chronic lymphocytic leukemia presents a symmetrical general enlargement of external lymph nodes, commonly with some enlargement of liver and spleen and often with obvious enlargement of retroperitoneal nodes. The blood count may be typically leukemic, subleukemic or aleukemic.

In the typical case our preference is to irradiate first the external node masses, that is, each side of the neck, each axilla, and each groin. Each

such mass is given 100 to 300 r high voltage x-rays once, one area being treated at a time, and the patient being treated at intervals of one to three days depending on his condition. We then wait a few weeks, as a rule, to observe the effect on these external readily palpable masses, and the effect on the blood. Such a test cycle of treatment may be followed by considerable regression of the enlarged nodes and usually by a marked favorable change in the blood count. Anemia may disappear, the white cell count, if high, may fall to nearly normal, while the differential count may show a reversal of the polynuclear lymphocyte ratio to nearly normal.

Further treatment then depends on the condition of the patient. If his blood count is nearly normal and if he has no marked internal masses of nodes or marked enlargement of spleen or liver it may seem best to withhold treatment until such time as the blood count or signs of leukemic infiltration in some area reveal the need for more treatment.

Unless some special feature appears, ordinarily the next course of irradiation is given to the mediastinal and retroperitoneal nodes. By taking a zone about 10 centimeters wide extending along the midline axis of the trunk, anteriorly and posteriorly, and dividing it into an upper, middle and lower third, one can irradiate the main bulk of these deep nodes. To each of these six portals (three anterior and three posterior) is given 100 to 300 r of high voltage x-rays. The individual doses and the intervals between them are chosen according to the condition of the patient.

Subsequent courses of treatment may consist of repetitions of these cycles to external or internal nodes, or both, or particular fields such as liver or spleen or deep inguinal and iliac nodes may demand special attention. The leukemic forms are treated in the same way. In these cases, of course the blood count is of less value and one must depend largely on the responses of the known foci of disease. It would be quite misleading to gain an impression from this description of technique that a rigid routine is followed. Each case must be individualized and by no means all cases are treated in this way. For example in the so-called splenic type of lymphocytic leukemia in which there is a large spleen with but little or no enlargement of lymph nodes the treatment should begin by irradiation of the spleen.

Irradiation of the entire body has seemed to work very well in chronic lymphocytic leukemia and in some cases we choose to begin

the treatment by this method, and to rely mainly on it, using local irradiation rather as a supplement to care for especially prominent masses or infiltrations

In the rare cases of lymphocytic leukemia in which no enlargement of liver, spleen, or lymph nodes can be found, one would naturally think of general irradiation as a logical procedure

The emphasis, then, in the treatment of chronic lymphocytic leukemia is first on irradiation of lymph node areas, and second on irradiation of other foci of lymphocytic infiltration, wherever found. About 9 per cent will show a survival of five years or longer after treatment is begun as against the average survival of about two years, and some patients will live ten to twelve years or longer.

### CHRONIC MYELOCYTIC LEUKEMIA

The typical case of this disease presents an enlarged spleen, sometimes of huge dimensions, frequently some enlargement of the liver, and as a rule practically a total absence of signs of enlargement of lymph nodes. The general run of experience indicates that best results, at least in the beginning, are obtained by irradiation of the spleen. This may be done by various methods. At Memorial Hospital we commonly use high voltage x-rays to large ports anteriorly and posteriorly over the spleen, giving 25 to 100 r at a sitting and treating daily or every other day to a total of about 300 r over each of the two ports. In some cases the radium pack is used, giving 2000 milligram hours or less at a sitting, at a radium skin distance of 10 centimeters, to a total of 6000 milligram hours anteriorly and posteriorly.

Such a course of irradiation may be followed by a transient increase in the leukocytosis, but in general, in about a month, a striking improvement will be found in the patient. He may gain weight, lose symptoms, present a marked shrinkage of the spleen, so that in some cases it may no longer be palpable, and his blood count may be restored so nearly to normal that it would be difficult to make a diagnosis of leukemia. In 3 weeks there may be an increase of a million red cells in the count.

Danger lies in overdosage of the more acutely ill patients. When external lymph nodes are enlarged, they may portend a more acute course. Signs of hemorrhagic tendency are danger signals, and indicate caution. Yet this bleeding tendency may disappear after irradiation.

Most of the writers state that it is advisable to be content to reduce

the white cell count to 20,000 or 30,000. If, however, our first cycle of treatment can succeed in bringing the count down to a normal level, I believe the patient as a rule will have a more nearly complete restoration to health for the time being and a longer interval before another course of treatment becomes necessary.

The blood count ordinarily gives the first sign that the disease is becoming active again and should be taken at intervals of seldom more than three weeks, at least at first. Further treatment is very much a matter of individualization. Some cases may carry on for years in response to repeated courses of irradiation given only to the spleen when it re-enlarges. In other cases special features arise, demanding special treatment. In some cases the blood count deteriorates again to a degree demanding more treatment at a stage when liver and spleen remain reduced to nearly normal size. At such times we consider either irradiation of the bones, especially spine, sternum, and proximal ends of long bones or irradiation of the entire body in small dosage. We are especially likely to think of irradiation of the bones in cases in which pains are felt about the bones and joints.

In some cases the spleen fails to shrink satisfactorily after a few cycles of treatment have been given to the spleen, and even after further irradiation it remains large and firm. Some authors report shrinkage of these refractory spleens after irradiation of the entire body. We have not confirmed these observations, but see no reason to doubt that such an effect may be possible. Adjuvant methods of treatment such as administration of arsenic, heliotherapy and transfusions are regarded as outside the scope of this paper.

*Results* Sooner or later every case becomes refractory to treatment. On the average these patients die in about two or three years after treatment is begun. Some survive exceptionally long periods even up to fifteen or twenty-five years, but in these cases one feels that there is some exceptional factor promoting longevity and that the treatment may have had relatively little to do with the long survival. Only a small percentage (about 6 per cent) of the patients with myelocytic leukemia survive over five years after beginning treatment. The chief value of irradiation in this disease lies in the fact that it can bring about remissions repeatedly, to an extent which would not ordinarily occur so that the patient, during his remaining span of life short though it may be, enjoys periods of comparative health which otherwise he could not have.

## POLYCYTHEMIA VERA

Polycythemia vera or erythremia may be regarded as an analogue of myelocytic leukemia, that is, as a disease in which the red cell series rather than the granulocytic series is stimulated to increased activity. It has been advocated that in erythremia the enlarged spleen should be regarded as serving a protective function and that therefore it should not be irradiated, that, on the contrary, all the treatment should be directed to the bone marrow, which is the primary seat of the disease. The same argument might seem to apply to myelocytic leukemia, yet general experience has shown that in that disease irradiation of the spleen as a rule gives results superior to those obtained by treatment of the bones. However, in treating erythremia by local irradiation we do now as a rule, direct our radiation to the bones (spine, sternum and ends of long bones). Sgalitzer and others claim excellent results in erythremia by systematic total body irradiation. Sgalitzer reported good results in forty-two of forty-four cases, stating that in the recurrences one and one-half to five and one-half years later he obtained just as good response as in the first cycle of total irradiation, and that these recurrences took place much later than after the expensive, time-consuming cycles of local irradiation of multiple fields.

However, in this field there are certain cases termed erythroleukemia in which usually the dominating features at first are those of erythremia, but in which the spleen may be unusually large, the white cell count unusually high and the percentage of myelocytes in the blood count unusually great. In such cases the red cell count may fall after some months, so that instead of polycythemia the patient develops an anemia and then the features of myelocytic leukemia may begin to predominate. In such cases we find that treatment of the spleen may be more efficacious than treatment of bones in relieving symptoms.

## SUMMARY

In summary, the problems of treatment of the lymphomatoid diseases are many and complex, by reason of the great diversity of lesions in this group of maladies. Here are presented the main principles which currently seem to me best to follow in caring for the more typical forms by means of irradiation.

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## BIOLOGICAL OXIDATION AND VITAMINS

*Harvey Lecture, May 18, 1939*

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As you know, the ultimate source of all energy, sustaining life, is the radiant energy of the sun. The energy of the sun's rays is captured by the green dyestuff of plants, the chlorophyll. This radiating energy cannot, as such, support life, for if it were essential, life would fail at night. Thus the energy is used to build up carbohydrate molecules from carbon dioxide and water, the excess of O being sent back into the atmosphere as  $O_2$ . In essence these carbohydrate molecules represent small parcels of energy, which can be stored and released by the cell according to needs. The "unpacking" of these parcels is the reverse reaction, in which the carbohydrate molecule is united again with oxygen to form carbon dioxide and water. This process we call oxidation or combustion. This oxidation is thus the ultimate source of all our energy. Since all cellular functions consume energy, oxidation is intimately connected with all activities of the cell and stands, so to speak, at the center of life.

During the last decades our conceptions regarding biological oxidation have been revolutionized and today oxidation represents one of the widest and most fruitful fields of biological research.

When speaking of oxidation we must always bear in mind one thing, i.e. that its purpose is to liberate energy and to liberate it in a form which can be used to maintain cellular functions.

Misled by the analogy of the steam engine, it was thought a few decades ago that in this process the molecule of foodstuff was simply attacked by oxygen, with the liberation of its energy in the form of heat. But there is this fundamental difference between the steam engine and our body: the latter is unable to use heat as a source of energy. Moreover, at the relatively low temperature of our body, oxygen does not attack the foodstuff molecule. It is evident that the process has to be activated in some way to take place at  $37^\circ C$ . It is natural that investigators looked first for an activation of oxygen, several active forms of oxygen being known to the chemist.

O Warburg proved first that the oxygen is "activated" in cells. He studied the effects of cyanide, a poison which stops biological oxidation even at minimal concentrations. This substance has one peculiar property, and this is to form very easily coordination complexes with metal-atoms. Thus Warburg arrived at the conclusion that cyanide stops respiration by inactivating certain metal-atoms responsible for the activation of oxygen. These metal-atoms are linked to protein and these metal-proteids have the properties of an enzyme, the metal acting as the active prosthetic group. Warburg called this metal-proteid the "respiratory enzyme."

Somewhat later, H. Wieland, studying hydrogenation processes, arrived at another theory of respiration. It is known that organic molecules, having a double bond, can be made to take up hydrogen if treated with hydrogen in the presence of a catalyst, such as colloidal palladium. The metal combines with hydrogen and "activates" it. Wieland found that this process is reversible and H can also be detached from organic molecules in the presence of a suitable catalyst, if, instead of adding  $H_2$  to the system we add a substance that is capable of binding H, i.e. an "H acceptor." Detaching H from an organic molecule is an oxidation. Wieland arrived at the conclusion that biological oxidations proceed in a similar way in oxidizing the organic foodstuffs, their H's being "activated" and detached, provided there is a suitable "H acceptor" present. Molecular oxygen, in Wieland's conception, is such an "H acceptor," while the foodstuff molecule itself acts as an "H donor." The activating enzyme we call "dehydrogenase" according to Thunberg's nomenclature. The place of the lost H's in the foodstuff molecule is taken by H-OH, water. In this way the molecule, by repeated dehydrogenation and hydration, becomes richer and richer in oxygen, until it is completely oxidized.

But how does all this work from the energy standpoint? We must remember that the aim of oxidation is in the first place the liberation of energy. The detaching of hydrogen from the organic molecule does not liberate energy. Neither does the introduction of water yield energy. The whole energy of oxidation is liberated in the oxidation of the hydrogen. It is well known that the oxidation of hydrogen is one of the greatest energy yielding reactions of chemistry.

These are quite simple statements but their consequences are rather far-reaching. They tell us that Nature knows, in essence, but one fuel and this is hydrogen. All our food is essentially but a fixed form of hydrogen and all the energy which supports life is derived from its oxidation.



with the formation of water

We thus have the whole energy cycle the plant cell, with its chlorophyll stores the energy of the sun, separating the elements of water, fixing the hydrogen to a solid carbon chain and sending the oxygen back to the atmosphere. All cells cover their energy need by reversing the process, taking the hydrogen from the organic molecule and uniting it again with the oxygen from the air.

It was thought at one time that the two theories, the theory of Wieland and the theory of Warburg, were contradictory. My first modest step in this domain was to show that there was no contradiction and that in the animal cell "activated oxygen oxidized activated hydrogen."

The next step of development is linked with the name of D. Keilin, who rediscovered certain hemin derivatives, found many years before by MacMunn. Keilin called these substances "cytochromes" and showed in classic experiments that they are substances involved in respiration. As Keilin taught us, there are three cytochromes, A, B and C. Cytochrome C has been isolated and shown to contain an iron atom. Probably the other two likewise contain iron. The metal atom is the active constituent of the molecule. In respiration this metal is alternately oxidized and reduced from its higher to its lower valency (ferric-ferrous). The three cytochromes are shunted in series. A is oxidized by Warburg's enzyme, A oxidizes C and C oxidizes B (Ball, Laki). Then cytochrome B oxidizes the hydrogen of the foodstuff, the "H donator." The H's of the foodstuff thus do not react immediately with the oxygen. Oxygen and hydrogen are separated by the series of cytochromes and Warburg's enzyme. The latter I will refer to as "cytochrome-oxidase," for its function is to oxidize cytochrome.

It is worthwhile to consider for a moment the implications of these findings. Of what does the oxidation and the reduction of a metal-atom consist? What is the difference, let us say, between ferrous and ferric iron? The difference is that the ferrous atom contains one more electron than ferric. When the hydrogen is oxidized by the Fe of cytochrome B it gives over its electron to the metal. The hydrogen itself acquires thereby a positive charge and becomes a hydrogen ion and unites with OH ions present in water. The electron added to Fe is then transferred from metal to metal, i.e. from cytochrome to cytochrome, then to the cytochrome-oxidase, to be transferred eventually to oxygen. The oxygen, after having taken up four electrons, can unite with four hydrogen

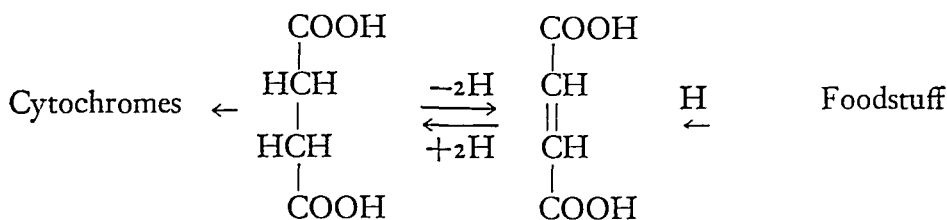


Fig 1

ions of the water to become two molecules of water. There is thus in the cell a whole chain of electron transfers in which the hydrogen of the foodstuff serves as an "electron donator," the oxygen serves as an "electron acceptor," while the cytochromes with their oxidase serve as "electron transmitters." The role of oxygen in respiration is thus limited to accepting the electrons. At every step the electron itself liberates a certain quantity of its energy. On this series of electron transfers about two-thirds of the total energy of oxidation is liberated.

To sum up, the hydrogen of the foodstuff is activated by the specific enzymatic activators, the "dehydrogenases," yields its electron to cytochrome and is transferred through the series of metals to oxygen. From the investigations of Thunberg we know a number of such dehydrogenases, which could activate the hydrogen of different foodstuff molecules. But is it really the sole function of dehydrogenases to split off the hydrogen of the foodstuff molecule and make its electron available to cytochrome? This was the question I asked myself a number of years ago. Studying the enzymes of muscle I was struck by the fact that there was one among these dehydrogenases which had specific qualities. Its resistance and kinetics (O type) were extraordinary and its activity amazing. This dehydrogenase was the succinodehydrogenase, the dehydrogenase of succinic acid, discovered long ago by Thunberg. How were we to explain that Nature should produce such an extraordinary enzyme for succinate, when we had no reason to believe that succinic acid itself was one of the principal foodstuffs? Aided by my faithful collaborators, Banga, Gozsy, Huszak, Laki, Straub and others, I arrived at the conclusion that the function of this enzyme was not to split off H from a foodstuff but to transfer H from the foodstuff to cytochrome. Succinic acid is activated and dehydrated by this enzyme to fumaric acid, the two free valencies being joined in the form of a double bond (Figure 1). Fumaric acid is likewise activated by the same enzyme, the "succino-

is one of the most fundamental chemical processes in Nature. As I will show you later, the same dicarboxylic acids probably also play a fundamental role in the respiration of plants.\*

Further development in this field is linked with the discovery and analysis of the codehydrogenases. Some fifteen years ago I observed that certain dehydrogenases, as the dehydrogenase of lactic acid, acted only in the presence of a thermostable substance. This coenzyme was later purified in my laboratory and found to be a nucleotide. von Euler and Nilsson showed that Euler's "cozymase," likewise a nucleotide, was capable of acting as codehydrogenase. But real progress was made when Warburg discovered that this codehydrogenase contained a pyridine derivative, nicotinic acid amide. This pyridine acted as an H acceptor, one of its double bonds being hydrogenated. Apart from the succinodehydrogenase, all dehydrogenases acting in the main respiration cycle seem to need codehydrogenase.

These findings not only lengthen the known chain of oxidations but also throw a new light on the nature of dehydrogenases. We must now look upon a dehydrogenase, like the malic-, lactic- or triose-phosphoric-dehydrogenase, as upon a specific protein which is capable of adsorbing and activating simultaneously two substances, and of causing two H atoms to pass from one to the other. If we take the oxidation of triose-phosphate, the first thing that happens is that this sugar is adsorbed and activated by a specific protein, the dehydrogenase. At the same time the coenzyme is also adsorbed and activated, two H's pass from the sugar to the coenzyme and we obtain oxidized sugar and dihydro-coenzyme. Now the dihydro-coenzyme is adsorbed by the maliccodehydrogenase together with oxaloacetate and the two H's pass from the dihydro-coenzyme on to the oxaloacetate and we obtain coenzyme and dihydro-oxaloacetate, i.e. malate. Now malate again gives its two H's to the coenzyme, and the coenzyme transmits them to fumarate.

At this point we get into difficulty, for the dehydrogenase that activates fumarate (the succinodehydrogenase) does not activate coenzyme

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\* Lately the role of H transporters of the  $C_4$  dicarboxylic acids has been denied by H. A. Krebs who believes that these acids act only as members in a more complicated cycle of carbohydrate breakdown. Krebs is of the opinion that oxaloacetate combines in muscle with an oxide of triose to citric acid, and the citric acid oxidizes to succinate. The succinate is oxidized to oxaloacetate, and the cycle begins again. I am unable to accept Krebs' generalization. Even if this cycle exists, it represents, as shown by Thomas, only an additional function of the  $C_4$  dicarboxylic acids.

As I pointed out two years ago a member of the chain was missing at this point which had to transmit H from the dihydro-coenzyme on to fumarate I suggested that this "something" might be a "yellow enzyme" These "yellow enzymes" are specific proteins which hold adsorbed a yellow alloxasine dye, which was observed first in my laboratory Later it was shown by Warburg that these dyes acted in conjunction with specific proteins Recently F B Straub, working in Keilin's laboratory, has isolated such an alloxasine protein which seems to answer all the requirements Its exact place in the oxidation chain is not yet ascertained, but probably it is identical with the alloxasine protein, tentatively postulated two years ago between malate, the dihydro-coenzyme and fumarate, respectively Straub's substance is also identical with the substance described by von Euler and Adler as "Diaphorase" and by Green and Dewan as "coenzyme factor" Unfortunately, time is too short to enter into detailed discussion of these catalysts, but I hope that this incomplete description brings out the point that the mechanism of biological oxidation represents a very complicated chemical apparatus of high complexity, specificity and precision This mechanism liberates the energy of the H piecemeal, shifting the H atoms of the foodstuff molecule from substance to substance, then detaches the electron of H, and sends it through a series of metals to oxygen, liberating in this way the energy of the electron in appropriate small quantities fit to be used by the cell for its different functions

I am hoping that you will forgive me if I do not present on this occasion an impartial review of the problems of oxidation, but instead present the development of the field from the narrow angle of my personal experience, giving undue prominence to my own work To take this wholly personal outlook I must confess that in starting in this field some fifteen years ago my primary interest was not oxidation at all What I really wanted to know was the function of the adrenal cortex At that time we knew next to nothing about it We only knew that man could not live without adrenals and turned brown before dying You all know that one of the typical symptoms of adrenal cortical deficiency, or Addison's disease, is the brown pigmentation of the skin and mucous membranes Now about half of the plants, including potatoes apples, pears and bananas, do the same thing they turn brown when dying I have always been convinced of the fundamental chemical unity of living Nature and I thought that the brown pigmentation in dying plants and

in patients with Addison's disease might have a common chemical foundation. In regard to the pigmentation of plants we knew from Palladin's work that it is connected with the disturbance of biological oxidation systems. Consequently, I decided to take up the study of oxidation, hoping that if I understood oxidation better I also would understand the adrenal gland.

It was known that the brown pigmentation of dying plants was connected with the activity of a specific enzyme, a polyphenoloxidase which oxidized polyphenols, mostly catechol derivatives. Different theories were presented concerning the mechanism of this action. I was able to show that the enzyme simply oxidized the polyphenol into the corresponding diquinon, taking off its two H's (Figure 4). The diquinon, if not reduced with sufficient rapidity, combines with proteins or amino acids to form highly colored melanoid substances.

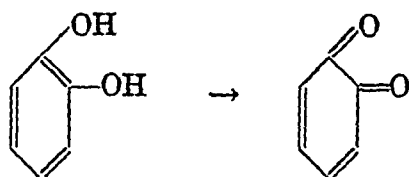


Fig. 4

The enzyme itself, the polyphenol, was lately isolated by Kubowitz in Warburg's laboratory and shortly afterwards by Keilin and was found to be a metal-proteid of copper.

This system, however, did not explain to me the function of the adrenal gland. So I turned the question around and did not ask why patients with Addison's disease turned brown, but why it was that we, who had normal adrenals, remained unpigmented. This could not be learned from the polyphenoloxidase plants, so I started to analyze the respiration of other plants which failed to turn brown when dying. About half of the plants, such as lemons and cabbages, do not turn brown when dying.

I soon found that the juice of these plants not only failed to turn brown itself but also prevented the juice of the polyphenoloxidase plants from turning brown, when the two juices were mixed. The inhibition was not complete, lasting only a few seconds, but was distinct. The analysis showed that this inhibition was due to the presence of a substance with peculiar properties which greatly fascinated me. The most striking

feature of this substance was its strong reducing power. It contained two very labile H atoms which explained the inhibition of pigment formation. By means of its two H's the substance reduced the quinols to phenol again, reversing the reaction shown in Figure 4.

The substance was crystallized and analyzed to a certain extent. I will not dwell upon details of its history for you all know it today as ascorbic acid, and you also know that it is identical with vitamin C. One of the most exciting phases of that research was the discovery of a rich source of ascorbic acid in Hungarian red pepper, the discovery of which made the preparation of several pounds of the pure vitamin possible. This substance was distributed to all workers desirous of investigating it, and their collaboration led in a short time to the complete analysis and synthesis of the vitamin. That highly spirited international collaboration of those days is still one of my pleasantest scientific memories.

Along with ascorbic acid I found in some plants an enzyme which could oxidize the acid in a reversible way and seemed to be involved, together with ascorbic acid, in respiration. The existence of this enzyme is denied in some quarters but I find it difficult to accept this conclusion.

This ascorbic acid oxidase has not yet been isolated. It is probably a Cu protein, as is the polyphenoloxidase.

To reduce  $O_2$  to water we need four electrons and four H ions. Thus to reduce oxygen to water the enzyme would have to hold the  $O_2$  molecule till it took up four electrons. Cu is unable to do this and will release the  $O_2$  after it has taken up two electrons and two H ions, and is thus reduced to  $H-O-O-H$ , hydrogen peroxide. Whenever the oxidation of a substance like a polyphenol or ascorbic acid is catalyzed by copper or a copper-proteid there is a formation of peroxide. Accordingly, in the presence of ascorbic acid oxidase and polyphenoloxidase we find a second enzyme, a peroxidase, which will react with the peroxide and utilize this peroxide for the oxidation of a second molecule of catechol or ascorbic acid. To sum up catechol-oxidase will oxidize two atoms of H from a molecule of catechol in the presence of  $O_2$ . The catechol is oxidized to quinon (Figure 4), while the  $O_2$  is reduced to peroxide  $O_2 + C_6H_4(OH)_2 = H_2O_2 + C_6H_4O_2$ . The  $H_2O_2$  thus formed will react with peroxidase and oxidizes a second molecule of catechol  $H_2O_2 + C_6H_4(OH)_2 = 2H_2O + C_6H_4O_2$ . The reaction in the case of ascorbic acid oxidase is analogous, except that the peroxide with the peroxidase will oxidize a phenol and the oxidized phenol in turn will oxidize a second molecule of

ascorbic acid These phenols are specific, are members of the group of the yellow benzopyrane dyes studied by Kostanecky and Perkins, and are called, according to their structure, flavones, flavanols or flavanones

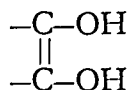
I have talked at such length about these reactions because we found that these dyes acting together with ascorbic acid also had a therapeutic potency which had certain characteristics of a vitamin action We tentatively called these substances vitamin P However, we were unable to demonstrate the vitamin nature conclusively in the animal experiments Our own observations on guinea pigs were not corroborated Beyond doubt the therapeutic action of these substances, which is capable of restoring the normal resistance of damaged capillaries, makes them available for the treatment of disease (vascular type of hemorrhagic purpura) for which medicine hitherto has had no remedy

But to come back to oxidation, there was something disquieting in these results In all systems hitherto discussed the action of  $O_2$  was catalyzed by a metal or series of metals The metal then oxidized reversibly two H atoms of an organic substance In the muscle this substance was succinic acid In certain plants it was catechol, in others ascorbic acid It would be difficult to find three more heterogeneous substances and we were unable to give any reason why Nature selected these particular compounds for this end Moreover, a greater uniformity was to be expected in such a fundamental process as oxidation Another very disquieting matter was that in spite of all this work we did not know how plants really respired I do not want to lose myself in details and will limit myself to telling you that there were serious reasons for believing that neither the polyphenoloxidase, nor the ascorbic acid oxidase were really involved in respiration and so we had no idea how plants respired, what the enzyme was which interacted in plants with  $O_2$  and what the substance was on which this enzyme acted

It became evident that something of basic importance was still to be learned To find out what this was, my faithful collaborators and I set out to study the catalytic action of metals which catalyze the dehydrogenating oxidation of organic molecules Such oxidations are catalyzed by metals outside the cells, and when the cell used metals to catalyze oxidation it did not invent a new principle, it merely applied an age-old reaction, but applied it in a very clever way linking the metal to a specific protein in the cell and thus giving it a chance to act at its best

There are two current theories to explain this catalytic activity of

metals The one is the very complicated radical theory of Haber The other theory is the simpler one According to the latter the metal simply oxidizes the H of the organic molecule, taking over its electron The metal thus reduced gives this electron in a second reaction to oxygen To use different and simpler words, the function of the metal is to be alternately oxidized by the O<sub>2</sub> and reduced by the H We found that none of these theories explained the changes and what really happened was that the metal combined, by its coordinate valencies, with the anion of the organic substance to be oxidized By this combination both substances, the metal and the organic molecule, forming now a single molecule, are "activated" We obtain thus a complicated coordinative molecule in which the metal acts as a central atom Now the valencies of this metal combine with a molecule of O<sub>2</sub> Both the O<sub>2</sub> and the organic molecule to be oxidized are built thus by the metal into a single molecule Electrons are then transferred within this molecule via the metallic central atom from the organic molecule to the O<sub>2</sub> I will not go into the details of these reactions The important matter is that the organic molecule, which is to be oxidized, has to answer very strict specifications It must contain two OH groups at a certain distance, with a double bond between the C atoms holding these OH groups The most suitable formation is the dienol grouping



This formation is very unstable and thus very rare, and is found only in a very limited number of natural substances One substance in which it is found is catechol, where it is stabilized by the aromatic cycle Thus we are able to give an adequate reason why Nature applied catechol in this oxidation mechanism Another substance, containing a dienol group, is ascorbic acid, in which the dienol is stabilized by the acid-lactone ring Thus we can give the reason why Nature also applies this substance At the same time the apparent heterogeneity of catechol and ascorbic acid disappears, in essence both are dienols

There is a third relatively common substance containing the dienol group, dioxymaleic acid, in which the dienol formation is stabilized by the two neighboring COOH groups (Figure 5) If all our ideas were correct we would have to expect that this substance is also employed by Nature in oxidation mechanisms I shall now describe the last phases



of my most recent research Experiments of Banga, Philippot and myself show that of the twenty-five plants examined all contain an oxidase for dioxymaleinic acid In some plants the enzyme has a very striking activity It is the most active oxidase known There is reason to believe that in this enzyme we have found the way in which oxygen enters into vegetable respiration Furthermore, we hope that this enzyme will shortly give us the explanation why Nature in animal cells utilizes succinic acid If you compare the formulae of succinic acid (Figure 1) and dioxymaleinic acid you will observe that the two substances are closely related, dioxymaleinic acid being simply an oxide of succinic acid

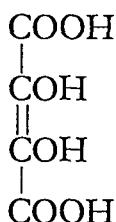


Fig 5

I cannot cover my subject completely, nevertheless, I hope that I have made clear the great changes that have taken place during the last decades in our conceptions regarding biological oxidation The field is hardly opened, but already it has given us a deeper insight into Nature's ways, it has yielded new substances, some of which are of vitamin nature and of great importance to health I have discussed alloxasines, the dye component of yellow enzymes, substances connected with H transportation and dehydrogenation The nicotinic acid amide of the codehydrogenases also acts as a member of the vitamin B group Vitamin C was crystallized in the course of an analysis of vegetable respiration The therapeutic action of Vitamin P was also discovered in the course of these experiments I should also have mentioned Vitamin B<sub>1</sub>, a substance which is closely connected with oxidative processes Oxidation studies have thus not only helped us to reveal the existence of new active substances but have also given us information concerning their exact function and have taught us to regard vitamins no longer as mysterious bearers of life and health but as simple little wheels in this wonderful chemical mechanism, the perfect functioning of which we call simply life and health These studies have also given us weapons for fighting disease and reducing human suffering, weapons not less sharp than the surgeon's knife

## THE DIAGNOSIS, TREATMENT, AND PREVENTION OF VITAMIN B<sub>1</sub> DEFICIENCY\*

NORMAN JOLLIFFE

### DIAGNOSIS

THE diagnosis of vitamin B<sub>1</sub> deficiency depends, at the present time, mainly upon a clinical evaluation of the history and the signs and symptoms presented by the patient. The clinical syndrome may be so typical that a positive diagnosis can be made, or so vague that it is difficult or even impossible to diagnose. It is hoped, however, that the clinician will soon have at his disposal a practical laboratory method to aid in the diagnosis.

The signs and symptoms attributed to vitamin B<sub>1</sub> deficiency are legion, the most definite being anorexia, fatigue, and a neurological and a circulatory syndrome. Anorexia and fatigue, are non-specific. In their presence the possibility of vitamin B<sub>1</sub> deficiency should be considered and confirmatory signs should be sought. When these symptoms occur without supporting objective signs, and do not definitely respond to thiamin therapy within seventy-two hours, they are probably not due to vitamin B<sub>1</sub> deficiency alone.

The neurological manifestations are those of bilateral and symmetrical polyneuritis involving first and predominantly the lower extremities. Peripheral neuritis that involves a single nerve, or that is not bilateral and symmetrical, or that does not involve first and predominantly the lower extremities is, in our experience, probably not due to vitamin B<sub>1</sub> deficiency alone. For such neuritides other etiologic agents should be sought.

For the purpose of clinical investigation we have classified the neurological manifestations according to severity into four groups: suggestive, mild, moderate, and severe. Heaviness of the lower extremities, and calf muscle cramps are usually the first symptoms.<sup>1</sup> These are followed by paresthesias in the toes and fingers, burning of the feet, and

\* Read February 2, 1939, at The New York Academy of Medicine in the Symposium on Vitamins with Special Reference to Therapy. From the Department of Medicine, New York University College of Medicine and the Medical Service of the Psychiatric Division, Bellevue Hospital, New York.

pain in the legs. It should be emphasized that pain, though nearly always present, can often be elicited only by a leading question. Calf muscle tenderness and plantar hyperesthesia are as a rule the earliest objective signs. The hyperesthesia may extend up the ankles and legs in a sock distribution. Vibratory sensation may be lost in the toes. These signs we classify as suggestive, and a positive diagnosis of polyneuritis is not made, as circulatory disturbances may cause these or very similar findings. When, however, in addition to these signs, the ankle jerks are absent, a diagnosis of mild polyneuritis can be made. As the deficiency continues, the sensory and motor changes advance, the knee jerks disappear, position sense in the toes becomes impaired, calf muscle atrophy develops, and foot drop follows. We classify this degree of involvement as moderate, provided the signs are confined to the lower extremities. When there is also involvement of the upper extremities, the spinal cord, or the cranial nerves, or when a "central neuritis" is present, we classify the polyneuritis as severe.

The circulatory manifestations of vitamin B<sub>1</sub> deficiency do not form a rigid clinical picture. They may occur in a person whose circulatory system is otherwise normal, or they may be superimposed on one previously damaged by degenerative, hypertensive, or inflammatory disease. These circulatory manifestations, as observed by Weiss and Wilkins,<sup>2</sup> Jones and Sure<sup>3</sup> and in our clinic,<sup>4</sup> may be classified as follows:

1. Edema and serous effusions occurring in the absence of congestive heart failure, enlarged heart, or recognized etiologic factors producing edema and serous effusions.

2. Edema and serous effusions occurring with supporting signs and symptoms of congestive heart failure, usually with definite roentgenographic evidence of cardiac enlargement.

3. Sudden circulatory collapse which may be the first manifestation of circulatory failure or may occur after other signs of circulatory failure are well advanced.

The circulatory manifestations of vitamin B<sub>1</sub> deficiency occur in about one-third of vitamin B<sub>1</sub> deficient subjects manifesting definite polyneuritis.<sup>4</sup> They are more likely to occur in subjects with suggestive or mild involvement than in those having advanced neuritis. This factor is related to the ability of subjects with mild neuritis to perform muscular exertion.

Some of the more characteristic diagnostic features of the circulatory

manifestations of vitamin B<sub>1</sub> deficiency are

- 1 Mild nature of the polyneuritis
- 2 Increased or normal velocity of the blood flow in the presence of congestive heart failure
- 3 Rapid response to specific therapy with complete and permanent reversibility of the circulatory manifestations

Vitamin B<sub>1</sub> deficiency should be suspected in the following groups of persons

- 1 The indigent and low income groups The average American diet affords a margin of safety in vitamin B<sub>1</sub> of 20 to 80 per cent <sup>5</sup> This safety margin, though below the optimum, provides sufficient vitamin B<sub>1</sub> to protect against deficiency polyneuritis under ordinary physiologic conditions As this diet is average, it follows that a considerable fraction of the American population must consume a superaverage and a considerable fraction a subaverage amount of vitamin B<sub>1</sub> That this is true is evident from calculations (Table I) made of the margin of safety of dietaries of families of wage earners and low salaried clerical workers living in industrial communities of the United States during 1934-36 <sup>6</sup> With the exception of one geographic group, families spending less than two dollars per week per capita for food are dangerously near or actually within borderline vitamin B<sub>1</sub>/calory ratios If this be true for wage earners, the indigent must consume even more of the cheap vitamin-free or vitamin-poor foods, such as sugar, white bread, rice, macaroni and other refined grain products

- 2 Persons who have erroneous dietary habits and food idiosyncrasies For example, the dietary history may reveal regular consumption of extradietary supplements of vitamin-free calories as obtained from sugar, corn syrup, alcohol, candy, pastries, or soft drinks, which may render a marginal diet inadequate In evaluating the adequacy of a diet we must also scrutinize the dietary of any subject who remembers what he has eaten The average person consuming a mixed dietary without food idiosyncrasies or restrictions rarely remembers this and is, therefore, probably consuming a varied diet The more varied the diet, the less likely it is to be inadequate

- 3 The alcohol addict These subjects often consume amounts of vitamin-free alcohol sufficient to lower the vitamin B<sub>1</sub>/calory ratio significantly, even if an otherwise adequate diet is maintained A smaller consumption of biologically good calories, and impaired absorption or

TABLE I

MARGIN OF SAFETY IN VITAMIN B<sub>1</sub> OF DIETS OF WAGE EARNERS AND LOW SALARIED CLERICAL WORKERS IN RELATION TO WEEKLY EXPENDITURE ON FOOD AND GEOGRAPHICAL SECTION\*

Region, number of families	Weekly Exp per food Const	VITAMIN/CALORY RATIOS			
		Thiamin N F calory	Safety Margin %	Vitamin B <sub>1</sub> calory	Safety Margin %
North Atlantic	1 33-1 99	0 308	+ 3	2 22	- 3
1394 white families	2 00-2 66	329	+ 10	2 54	+11
	2 67-3 32	370	+ 23	2 87	+25
	3 33-3 99	320	+ 7	2 97	+29
	4 00-4 66	404	+ 35	3 00	+31
Pacific	1 33-1 99	0 442	+ 47	2 85	+24
688 white families	2 00-2 65	363	+ 21	2 67	+16
	2 67-3 32	357	+ 19	2 95	+28
	3 33-3 99	349	+ 16	2 69	+13
	4 00-4 66	373	+ 24	2 84	+24
East South Central	0 67-1 32	0 256	- 15	2 30	- 0
426 white families	1 33-1 99	327	+ 7	2 19	- 4
	2 00-2 66	344	+ 15	2 37	+ 4
	2 67-3 32	391	+ 30	2 57	+12
South	0 67-1 32	0 318	+ 6	2 00	-13
284 Negro families	1 33-1 99	351	+ 17	2 31	+ 1
	2 00-2 66	339	+ 13	2 40	+ 5
	2 67-3 32	367	+ 22	2 69	+17
Sherman's Average American Diet		0 539	+ 80	2 74	+20
New York Budget Council	1 75	0 650	+113	3 08	+28

utilization of the vitamin, are additional factors leading to vitamin deficiency in these subjects

4 Patients having diseases altering the vitamin B<sub>1</sub> requirement The better known of these are listed in Table II The primary factors that raise the vitamin B<sub>1</sub> requirement are increased total metabolism, reduced absorption of the vitamin from the gastrointestinal tract, and increased excretion of the vitamin following absorption

\* Reproduced through the courtesy of *New International Clinics* <sup>5</sup>

TABLE II  
FACTORS INCREASING THE VITAMIN B<sub>1</sub> REQUIREMENT\*

I Increase in Total Metabolism	II Faulty Assimilation	III Increased Excretion
<p>A Abnormal activity, as associated with</p> <ol style="list-style-type: none"> <li>1 Prolonged strenuous activity</li> <li>2 Delirium</li> <li>3 Manic depressive psychosis, manic type</li> </ol> <p>B Fever, especially of long duration, as in</p> <ol style="list-style-type: none"> <li>1 Tuberculosis</li> <li>2 Typhoid</li> <li>3 Malaria</li> </ol> <p>C Hyperthyroidism</p> <p>D Pregnancy</p> <p>E Rapid growth</p>	<p>A Diarrhea, especially of long duration, as in</p> <ol style="list-style-type: none"> <li>1 Ulcerative and mucous colitis</li> <li>2 Intestinal parasites</li> <li>3 Intestinal tuberculosis</li> <li>4 Sprue</li> </ol> <p>B Gastrointestinal fistulae</p> <p>C Diseases of liver or gall bladder</p> <p>D Achlorhydria</p> <p>E Carcinoma of stomach</p>	<p>A Polyuria, as in</p> <ol style="list-style-type: none"> <li>1 Uncontrolled diabetes mellitus</li> <li>2 Diabetes insipidus</li> <li>3 Long continued excessive fluid intake, as in urinary tract infections</li> </ol> <p>B Lactation</p>

### TREATMENT

The treatment of vitamin B<sub>1</sub> deficiency consists of rest, diet, vitamin B<sub>1</sub>, and correction of the factors responsible for the deficiency

Because of the danger of circulatory collapse on exertion, rest is essential for all subjects showing evidence of moderate or severe vitamin B<sub>1</sub> deficiency, complete rest if the patient has severe polyneuritis or shows circulatory manifestations. Before we realized the importance of absolute bed rest, we had a few unfortunate accidents, the sequel of which was sudden death. This danger apparently ceases after a short period of adequate treatment. We, therefore, confine these patients to bed the first few days. But after a few days of thiamin therapy the patient is made ambulatory as soon as possible, in order to prevent shortened muscles and to obviate much physiotherapy.

During the last six years, working with Doctors Joffe, Colbert, Bowman, Goodhart, Rosenblum and Fein, we have attempted, among other things, to ascertain the most effective dose of vitamin B<sub>1</sub>, the most effective route, and the various factors modifying the response to thiamin.

\* Reproduced through the courtesy of *New International Clinics* 5

chloride For these studies we selected patients having a mild polyneuritis (the so-called "standard" subject), which, on the basis of history and of clinical characteristics, was thought to be due to vitamin B<sub>1</sub> deficiency

We are aware of the hazards of drawing conclusions from therapeutic results Improvement in these patients cannot as yet be gauged by a practical laboratory procedure Furthermore, polyneuritis due to vitamin B<sub>1</sub> deficiency is a chronic disease, subject to wide variations in degree of involvement, occurring in subjects who frequently have a multiple rather than a single deficiency and in whom the pathologic changes, because of extent or duration, may be so far advanced as to be irreversible For these reasons it was necessary to study a "standard" patient, whom we selected in accordance with the following criteria there should be no clinical evidence of other deficiency disease, the signs of polyneuritis must be limited to the lower extremities, with the knee jerks preserved and with no obvious muscle atrophy or foot drop, the patient must show absent ankle jerks plus some demonstrable sensory changes, such as calf muscle tenderness, skin hyperesthesia in a peripheral nerve distribution, and impairment of vibratory or position sense We judged the results of therapy on the basis of objective findings alone To minimize interpretation, the tendon reflexes were recorded only as being present or absent, and sensory changes were recorded as to extent but not degree

Since these studies have yielded useful hints concerning therapy, the results will be summarized

- 1 Improvement in objective neurological signs of vitamin B<sub>1</sub> deficiency does not result when a patient is maintained with a diet consisting of a vitamin B<sub>1</sub>/calory ratio of 1.7<sup>7</sup>

- 2 When large amounts of vitamin B complex (vitamin B<sub>1</sub> free), nicotinic acid, or riboflavin are added to diets containing a vitamin B<sub>1</sub>/calory ratio of 1.7 no improvement in objective neurological signs of vitamin B<sub>1</sub> deficiency occurs<sup>8</sup>

- 3 With constant diets rich in the vitamin B complex, the rate and degree of improvement in the objective signs of polyneuritis vary directly with the vitamin B<sub>1</sub> intake<sup>7,9</sup> This is illustrated in Table III

- 4 Diets containing a constant amount of vitamin B<sub>1</sub>, but rich in the entire vitamin B complex, apparently lead to a greater improvement in objective signs of polyneuritis than diets poor in vitamin B complex<sup>8</sup>

- 5 The fraction of the vitamin B complex responsible for this enhanced action of thiamin is not known We have evidence that it is not

TABLE III

## THERAPEUTIC RESPONSE OF THE "STANDARD" PATIENT TO VARYING DOSES OF THIAMIN CHLORIDE

<i>Vitamin B<sub>1</sub> as Thiamin Chloride</i>	<i>No of Days</i>	<i>Per cent Worse</i>	<i>Per cent Unchanged</i>	<i>Per cent Improved</i>	<i>Per cent Cured</i>
1 mg	21	40	60	0	0
2 mg	21	0	10	90	0
3 mg	21	0	0	100	40
3 mg	10	0	0	100	10
13 mg	10	0	0	100	50

riboflavin or nicotinic acid, and that it is not present in the highly concentrated fractions of liver extract effective in pernicious anemia <sup>8</sup>

6 Phosphorylated vitamin B<sub>1</sub> (or co-carboxylase) is apparently no more and no less effective than thiamin chloride <sup>8</sup>

7 Administration of thiamin chloride by the intrathecal route possesses no advantage over the intramuscular or intravenous route <sup>8</sup>

Using these facts gained from the study of our "standard" patients, and from the responses of our patients having moderate or severe manifestations of vitamin B<sub>1</sub> deficiency, we recommend the following dietary and specific treatment

1 Insure that the diet is adequate in all respects One of the best ways of doing this is to eliminate all vitamin-free or vitamin-poor foods such as white bread or crackers, pastries, alcohol, corn syrup, candy, corn starch, polished rice and soft drinks Yet the diet must be one that the patient can eat, digest and assimilate For patients who are extremely ill, the diet must be largely restricted to milk, cream, ground liver, pureéd legumes, thin whole grain cereals and fruit juices, administered if necessary through the nasal catheter in hourly feedings Following improvement, or in less severely ill patients, whole wheat bread or crackers is added, the legumes need not be pureéd, other vegetables and raw and cooked fruit are added, and a wider variety of meats permitted provided that 250 grams of either liver or pork muscle are included in one of the meals daily

2 Supplement the diet by vitamin preparations These supplements should include daily 50,000 international units of vitamin A, 400 to 500 mg of cevitic acid, and a rich source of the entire vitamin B complex



To insure the adequacy of the entire vitamin B complex, we routinely administer one of the following 20 grams of vegex, 60 grams of brewers yeast, or 30 grams of aqueous liver extract. We would like to stress that vitamin concentrates, especially those in pill or capsule form, are possibly lacking either quantitatively or qualitatively in one or more of the fractions of the vitamin B complex.

3 Administer thiamin chloride in adequate amounts. The specific therapy should be administered parenterally, erring on the side of wasting the vitamin rather than giving a suboptimal amount. If the patient is in circulatory collapse or in severe congestive heart failure, large amounts of thiamin chloride should be given, up to 1000 mg within the first twenty-four hours. The first dose may consist of 100 mg intravenously and 300 mg intramuscularly, with subsequent administration of 200 mg intramuscularly every three to six hours. During the second twenty-four hours the dosage of thiamin chloride should be reduced to amounts recommended for the less severely ill patients. This latter group can be treated safely, depending upon severity, by administration of 50 to 200 mg of thiamin chloride daily, preferably given in two doses, intramuscularly. After the patient is saturated with thiamin chloride, the amount of thiamin may be reduced to 10 mg daily till convalescence is well established. Saturation may be recognized by the detection of a distinct odor resembling burnt rubber in the urine. Following convalescence, the balanced diet supplemented by rich sources of the vitamin B complex is sufficient unless a complication exists requiring an unusual amount of vitamin B<sub>1</sub>, in which case thiamin chloride should be continued in amounts of 5 to 10 mg daily.

The underlying cause primarily responsible for the deficiency must be found and if possible eradicated. It may be an inadequate diet, an underlying alcoholism, or some disease preventing the absorption or utilization of the vitamin.

#### PREVENTION

The prevention of vitamin B<sub>1</sub> deficiency consists of insuring an adequate intake of this vitamin. This problem may be met in at least three ways for the general population. The first and best solution would be the substitution of whole wheat bread and whole grain cereals for white bread and refined cereals, plus a reduction in our annual per capita consumption of vitamin-free sugar and vitamin-free alcohol.

A second possible solution would be the addition to vitamin B<sub>1</sub> deficient foods of enough thiamin chloride to bring the vitamin B<sub>1</sub>/calory ratio above borderline levels. Approximately 0.5 mg of thiamin chloride for each 1000 calories would provide a sufficient margin of safety. The cost of this added thiamin to the manufacturers would probably not be in excess of one-quarter cent per 1000 calories. This method would not replace other nutritional factors removed in the milling and refining processes.

The third method would be for each individual consuming a sub-optimal diet to take a daily supplement of either 2 mg of thiamin chloride, or, preferably, a preparation of the entire vitamin B complex containing the same amount. The latter method would be impractical for a large portion of our population because of the expense of these preparations. The first two suggestions could be carried out with little added cost to the consumer.

The prevention of vitamin B<sub>1</sub> deficiency in persons in ill health consists of the recognition of the factors that alter the vitamin B<sub>1</sub> requirement, followed by the administration of prophylactic amounts of vitamin B<sub>1</sub>. The administration of vitamin B<sub>1</sub> alone to those in ill health may not be sufficient, and we therefore recommend the use of the entire vitamin B complex plus 5 to 10 mg of thiamin chloride daily, as well as other accessory elements of nutrition. In diseases interfering with absorption, the parenteral route should be utilized. A hitherto unrecognized danger exists of inducing vitamin B<sub>1</sub> deficiency in patients maintained with parenteral feedings of glucose, as in postoperative conditions. For such patients, this danger can be prevented by the routine administration of 5 to 10 mg of thiamin chloride.

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## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

FEBRUARY 2—*The New York Academy of Medicine* Executive session—Reading of the minutes ¶ Papers of the evening, Symposium on vitamins with special reference to therapy—a] Vitamin A, Arthur M Yudkin, Clinical Professor of Ophthalmology, Yale University School of Medicine, b] Vitamin B, Norman Jolliffe, Assistant Professor of Clinical Medicine, New York University College of Medicine, c] Vitamin C, Gilbert Dalldorf, Director of Laboratories, Grasslands Hospital, Valhalla, Discussion by Arthur J Patek, Jr, Somer Weiss, Boston, Philip Finkle ¶ Report on election of members

FEBRUARY 16—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The Fifth Harvey Lecture, "The pathology of rickets with particular reference to the changes at the cartilage shaft junctions of the growing bones, Edwards A Park, Professor of Pediatrics, The Johns Hopkins University School of Medicine

MARCH 2—*The New York Academy of Medicine* Executive session—Reading of the minutes ¶ Papers of the evening—Symposium on arthritis—a] Gout, Philip S Hench, Professor of Medicine, University of Minnesota (Mayo Foundation), b] The nature of hypertrophic arthritis (degenerative joint disease), Walter Bauer, Associate Professor of Medicine, Harvard University Medical School, c] Rheumatoid arthritis The problem of diagnosis and treatment, Ralph H Boots, Associate Attending Physician, Presbyterian Hospital, Discussion by Philip D Wilson, Edward F Hartung, Albert B Ferguson ¶ Report on election of members

An exhibit was held in connection with the Stated Meeting It was arranged by Dr Albert B Ferguson and consisted of various arthritides selected to compare and contrast the distinctive features of rheumatoid arthritis, osteoarthritis, gout, tuberculosis, suppurative arthritis and gonococcal arthritis in various states of these diseases and at various joints with particular reference to their differences

in type of destruction, decalcification, calcification and soft tissue reaction

Chemistry, University of Szeged, Hungary

MARCH 16—*The Harvey Society (In affiliation with The New York Academy of Medicine)* The Sixth Harvey Lecture, Distribution of enzymes in tissue and cells, K Linderstrom-Lang, Carlsberg Laboratory, Copenhagen

APRIL 6—*The New York Academy of Medicine* Executive session—a] Reading of the minutes, b] Election of Trustee ¶ The fourteenth Hermann Michael Biggs memorial lecture was delivered by Mr Frederick Osborn, Research Associate in Anthropology, American Museum of Natural History on "The significance to medicine of present population trends" ¶ Report on election of members and corresponding fellows

APRIL 20—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The Seventh Harvey Lecture "Genetic and hormonal factors in some biological processes", C H Danforth, Professor of Anatomy, Stanford University

MAY 4—*The New York Academy of Medicine* Executive session—a] Reading of the minutes, b] Presentation of diplomas ¶ Papers of the evening—Symposium on recent advances in the treatment of peripheral vascular disease—a] Clinical manifestations (25 min), Irving S Wright, Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, b] Medical treatment (25 min), Edgar V Allen, Assistant Professor of Medicine, University of Minnesota (Mayo Foundation), c] Surgical treatment (25 min), Reginald H Smithwick, Assistant in Surgery, Harvard Medical School, Discussion, Beverly Chew Smith (8 min), James C White, Boston (8 min) ¶ Report on Election of Members

MAY 18—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The Eighth Harvey Lecture, "Biological oxidation and vitamins," Albert Szent-Gyorgyi, Professor of Medical

## SECTION MEETINGS

FEBRUARY 3—*Surgery* Papers of the evening —a] The Miller-Abbott tube as an adjunct to surgery of small intestinal obstruction, Octa Leigh and John A Nelson (by invitation), Discussion by Henry Graham, b] The use of vitamin K and bile salts in the prevention and control of the bleeding tendency in obstructive jaundice, Kenneth B Olson (by invitation), Discussion by Robert Moore, c] The treatment of staphylococcus septicemia with bacteriophage, Alfred Longacre and Helen Jern (by invitation), Discussion by Ward Mac Neal, d] The study of wound healing of transverse and vertical incisions in 400 operations on the biliary tract, John Gius and Howard Barkley (by invitation), Discussion by Beverly Smith, e] Electro-Thermic coagulation of aortic aneurysm, Arthur H Blakemore (by invitation), Discussion by Robert Levy

FEBRUARY 7—*Dermatology and Syphilology* Presentation of cases—a] Vanderbilt Clinic, b] Miscellaneous cases ¶ General discussion ¶ Executive session

FEBRUARY 7—*Pediatrics* Presentation of case—Adjustment problems in an adolescent boy, Norvelle C LaMar (by invitation) ¶ Round table discussion—The problems of adolescence, Herbert B Wilcox, Chairman, Beatrice V Kesten, Norvelle C LaMar (by invitation), Howard C Taylor, Jr, and by invitation Mr Lawrence K Frank, Vice-President, The Macy Foundation, Mrs Millicent Carey McIntosh, Principal, The Brearley School, Mr James I Wendell, Headmaster, The Hill School

FEBRUARY 14—*Neurology and Psychiatry* Reading of the minutes ¶ Papers of the evening—a] Further investigation on affect and skin temperature, Bela Wittelmann (by invitation), Harold G Wolff, Discussion by Frank Fremont-Smith, Paul Schilder, b] Electroen-

cephalography and pneumencephalography—a comparative study, Leo M Davidoff, Margaret Rheinberger (by invitation), Discussion by Cornelius G Dike, Kurt Goldstein (by invitation), Armando Ferraro, Foster Kennedy, c] A new approach to the treatment of epilepsy, Manfred Sakel (by invitation), Discussion by Foster Kennedy, Emanuel D Friedman, Irving H Pardee

FEBRUARY 15—*Otolaryngology* Reading of the minutes ¶ Papers of the evening—Peroral endoscopy—a] Inception and development, M C Myerson, b] Anesthesia, R L Moorhead (by invitation), c] Bronchoscopic clinic, David Jones, d] Indications for 1 Laryngoscopy and bronchoscopy, Rudolph Kramer, 2 Esophagoscopy, gastroscopy and duodenoscopy, Charles J Imperatori, e] Contraindications and accidents, John D Kernan, f] Single and biplane fluoroscopy, F M Law, g] Pneumograms, technic and interpretation, George R Brighton

FEBRUARY 15 — *Genito-Urinary Surgery* Reading of the minutes ¶ Case reports—a] Ruptured aortic aneurysm, simulating renal tumor, Saul J Pearlman (by invitation), b] Carcinoma of the adrenal cortex with adrenocortical syndrome, Report of two cases, Joseph Lenenbaum ¶ Paper of the evening—Renal, perirenal and pararenal suppurations, John Duff, Discussion by Joseph A Hyams, Howard S Jeck, Paul Aschner, Gordon Oppenheimer, Isidore Rubin ¶ General discussion

FEBRUARY 17—*Orthopedic Surgery* Reading of the minutes ¶ Presentation of cases ¶ Papers of the evening—a] Subdeltoid bursitis treated by aspiration and vascularization, Joseph E Milgram, Discussion by Leo Mayer, b] Painful shoulders, Robert L Patterson, c] Value of electrical treatment of subdeltoid bursitis, Norman E Titus ¶ General discussion ¶ Executive session

FEBRUARY 20—*Ophthalmology* Examination of cases, 7 00 o'clock (bring instruments) ¶ Reading of the minutes 8 15

¶ Case reports—a] Contact glass correction of monocular aphakia with binocular single vision, A E Town (by invitation), b] Fuchs absorption stripes of the cornea, Joseph Laval, c] Subconjunctival injections of neo-prontosil in the treatment of eye infections, R Townley Paton, d] Altitudinal hemianopsia associated with absence of radial pulse bilateral, H W Brown (by invitation), e] Relation of vascular disease to retinitis A new clinico-pathological study (with slides), S A Agatston, f] Unilateral lachrymation associated with chewing, Philip Adalman (by invitation), Discussion by Morris Bender (by invitation), g] Herpes zoster ophthalmicus (left), Frances Richman (by invitation), h] Keratoconjunctivitis with pannus associated with acne rosacea, Conrad Berens, Paul McAlpine (by invitation), i] Fundus presentation with retinitis striata, Olga L Sitchevska (by invitation), j] Bilateral cystoid detachment of the retina, A L Kornzweig (by invitation), k] Paralysis of the superior rectus in Graves' disease, Saul Miller (by invitation), l] Optic neuritis of rhinologic origin, Morris Jaffe, m] A cyst in the vitreous, Frank LaGattuta (by invitation)

FEBRUARY 21—*Medicine* Reading of the minutes ¶ Papers of the evening—a] Mechanism of nephritis induced by anti-kidney serum, Joseph E Smadel, Rockefeller Hospital (by invitation), Discussion by Lee E Farr, Rockefeller Hospital (by invitation), b] Acute nephritis in relation to hemolytic streptococcus infection, John D Little, Discussion by A R Dochez, c] The renal and vascular sequelae of glomerulonephritis, George Braehr, Discussion by Dana W Atchley

FEBRUARY 28—*Obstetrics and Gynecology* Presentation of cases—a] Repair of prolapse in the senile without anesthesia (two cases), David N Barrows ¶ Papers of the evening—a] A modification of the Manchester operation (illustrated by motion pictures), Paul A Younge, Boston (by invitation), Discussion by Robert T Frank, Harvey B Matthews



b] Management of breech presentation, read by Christopher J. Duncan, Brookline (by invitation), Discussion by James A. Harrar (by invitation), William E. Studdiford ¶ General discussion

**SURGERY** Instead of the regular meeting on March 3, the Section of Surgery held a combined meeting with the Section of Medicine on March 21,

**MARCH 7—Dermatology and Syphilology** Presentation of Cases—a] Skin and Cancer Unit of Post-Graduate Medical School, b] Miscellaneous cases ¶ General discussion ¶ Executive session—Appointment of Nominating Committee

**MARCH 7—Joint Meeting, Neurology and Psychiatry and the New York Neurological Society** Papers of the evening—a] Colloid tumor of the third ventricle with a concomitant large sella turcica, with necropsy findings, M. Neustädter, Theodore Meltzer (by invitation), Discussion by Joseph H. Globus, b] Observations on the position of the motor cortex in man, obtained through electrical stimulation, John E. Scarff, Discussion by Foster Kennedy, c] Frontal lobectomies in the treatment of tumors in the anterior cranial fossa, Byron Stookey, Discussion by M. H. Teitelbaum (by invitation), Richard Brickner, Ira Cohen ¶ Executive session—Section of Neurology and Psychiatry, Appointment of Nominating Committee

**MARCH 8—Historical and Cultural Medicine** Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one Member of Advisory Committee ¶ Papers of the evening—a] Medicine and Surgery—Its study and practice in the United States before 1860, William C. Clarke, Cornwall Bridge (by invitation), Discussion by Paul B. Sheldon, Hugh Auchincloss, b] Nathan Smith and cancer therapy, Ashley W. Oughterson, New Haven (by invitation), Discussion by Cornelius P. Rhoads ¶ General Discussion

**MARCH 9—Pediatrics** Symposium on treatment of bone injuries in infancy and

childhood presented by the staff of the fracture service of the Presbyterian Hospital ¶ Reading of the minutes ¶ Papers of the evening—a] Fractures of the clavicle, Harrison L. McLaughlin (by invitation), b] Supracondylar fractures, Frederick M. Smith (by invitation), c] Reliance on growth correction of deformities, Barbara B. Stimson, d] Epiphyseal injuries, Clay Rav Murray, e] First aid treatment, William Darrach ¶ General discussion ¶ Executive session—Appointment of Nominating Committee

**MARCH 15—Genito-Urinary Surgery** Reading of the minutes ¶ Case reports—a] Chorioepithelioma of bladder, J. M. Szilagyi (by invitation), b] Solitary kidney with anuria (three cases), Leo Edelman, H. E. Leiter (by invitation), c] Diverticulum of female urethra, H. E. Leiter (by invitation), d] Uretero-vesical reimplantation of ureter, Abraham Hyman, e] Perirenal insufflation, William H. Mencher, f] X-ray control for operative treatment of renal calculi, G. Oppenheimer, g] A new medium for retrograde pyelography, M. Swick (by invitation) ¶ General discussion ¶ Executive session—Appointment of Nominating Committee

**MARCH 15—Otolaryngology** Instead of the regular meeting of the Section of Otolaryngology on March 15, at the Academy, the members of the Section were invited to a joint meeting with the College of Physicians of Philadelphia ¶ Papers of the evening—a] Speech hearing, Douglas MacFarlan, Discussion by Edmund P. Fowler, b] Sensitization reactions as observed microscopically in the living mammal, Elliot R. Clark, Eleanor Linton Clark, Richard G. Abell, Ph.D., Harry Schenck Discussion by Marvin F. Jones

**MARCH 17—Orthopedic Surgery** Reading of the minutes ¶ Presentation of case—Hemiphalangectomy in hallux valgus and hallux rigidus, Albert J. Schein, Discussion by Seth Selig, Robert Lippmann ¶ Papers of the evening—a] Tubercu-

lous arthritis Study of 100 operated cases, B M Bosworth, Discussion by Mather Cleveland, b] Slipped femoral epiphysis treated by ambulatory spica, Max S Rabinowitz, Discussion by Samuel S Kleinberg, c] Results of amputation for tuberculous knee foci, E M Winant, Discussion by Arthur Krida General discussion ¶ Executive session—Appointment of Nominating Committee

MARCH 20 — *Ophthalmology* Instructional Hour—After cataract, Webb Weeks Slit Lamp Demonstration, Milton I Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Reading of the minutes (8 30) ¶ Presentation of cases—a] Aspiration of the anterior chamber for glaucoma and other diseases of the eye, Conrad Berens, b] An unusual case of retained intraocular foreign body, Edgar P Sherman (by invitation), c] Bilateral congenital ectopia lentis, Edgar P Sherman (by invitation), d] Contralateral transillumination, Henry Minsky, e] Cysticercus cellulosis in the vitreous, Clyde E McDonald ¶ Paper of the evening—Further studies of the Canal of Schlemm and its anastomoses, Georgiana Dvorak-Theobald (by invitation) ¶ Executive session—Appointment of Nominating Committee

MARCH 21—*Combined Meeting, Medicine and Surgery* Papers of the evening—Medical and surgical aspects of the gastric ulcer problem—a] Natural history and diagnosis of gastric ulcer, T Grier Miller, Philadelphia (by invitation), b] The indications for surgical therapy of gastric ulcer, Fordyce B St John, c] Discussion (1) Pathology of gastric ulcer, Nathan C Foot, (2) The value in the control of treatment, R E Pound, (3) Medical management, Howard F Shattuck, (4) Surgical procedures Conduct W Cutler, Jr, d] Open discussion ¶ Executive session—Appointment of Nominating Committee

MARCH 28—*Obstetrics and Gynecology* Presentation of case—Unusually large tumor of the vulva, Joseph Q Jones (by invitation)

tion) ¶ Papers of the evening—a] Sulphamidamide treatment of gonorrhea in the female, Emily D Barringer and Staff, Kingston Avenue Hospital, Discussion by E A Horowitz (by invitation), B H Schoolnik (by invitation), b] Intravenous basergin in the third stage of labor (Report of 1500 cases), Edward J Davin (by invitation), Discussion by S J Scadron, c] Analysis of maternal deaths and hospital obstetrical statistics in New York County, Report of the Committee on Maternal Welfare, Max Schneider (by invitation), Discussion by George W Kosmak, Charles A Gordon (by invitation), John L Rice, Alfred M Hellman ¶ Executive session—Appointment of Nominating Committee

APRIL 4 — *Dermatology and Syphilology* Presentation of cases—a] City Hospital, b] New York Polyclinic Hospital, c] New York Hospital & Cornell Medical College, d] Miscellaneous cases ¶ General discussion ¶ Executive session—Nominations of Section Officers and one member of the Advisory Committee

APRIL 7 — *Surgery* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of the Advisory Committee ¶ Presentation of papers—a] The appendix stump its manner of healing both in the open and closed methods of treatment, Isidor Kross, Discussion by Percy Klingenstein, b] The importance of early diagnosis and treatment in acute appendicitis, Bronson S Rav Discussion by George J Heuer, c] The severer forms of acute appendicitis with special reference to appendiceal abscess, Ernest E Arnheim, Discussion by Eugene H Pool, d] Methods of drainage in appendicitis, F Stafford Wearn (by invitation), Discussion by Edward W Peterson ¶ General discussion

APRIL 11—*Neurology and Psychiatry* Papers of the evening—a] Vertebral fractures as a frequent complication in Metrazol therapy Phillip Polatim (by invitation), Murray M Friedman (by invitation),

Meyer M Harris, William A Horowitz (by invitation), Nolan D C Lewis (by invitation), Clay R Murray, b] Psychological factors in migraine, Herman Selinsky, Discussion by Abraham Kirdiner, Harold G Wolff, Lewis Stevenson, Emanuel D Friedman, George Hyslop, Bela Mittleman (by invitation), c] Case of cerebral "Pseudo Abscess" of otogenic origin, Emanuel D Friedman Discussion by E Miles Atkinson (by invitation), Charles Davison, Richard M Brickner, d] Sex taboos, sex offenders and the law, Joseph Wortis, Discussion by Donald Shaskan (by invitation), Ruth Benedict (by invitation), Adolf Meyer, Israel Strauss  
 ¶ Executive session—Nomination of Section Officers and one member of Advisory Committee

APRIL 13—*Pediatrics* Reading of the minutes ¶ Papers of the evening—a] Fetal lead poisoning in a nursing infant due to prolonged use of lead nipple shields, Murray H Bass, Sidney Blumenthal (by invitation), Discussion by John Caffey, Benjamin Kramer, Charles Hendee Smith, b] The use of tetanus toxoid in private practice, Robert Page Rogers Discussion by Edith M Lincoln, Samuel Z Levine, Abraham Tow, c] Puberty in the male, Physical development and endocrinopathies, William A Schoenfeld (by invitation), Discussion by Robert I Frank, d] Medical care of the non-hospital case of contagion, with special reference to the care of whooping cough, Harry O Zamkin (by invitation), Discussion by Bela Schick ¶ Executive session—Nomination of Section Officers and one member of the Advisory Committee

APRIL 17 — *Ophthalmology* Instructional hour — Plastic surgery, Wendell L Hughes ¶ Slit lamp demonstration, Milton I Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Executive session—a] Reading of the minutes (8 30), b] Nomination of Section Officers and one member of Advisory Committee ¶ Presentations—a] A

new implantation sphere made of vitallium, William Brown Doherty, b] Post operative report on a case of meningioma producing unilateral exophthalmos, James W Smith ¶ Paper of the evening The role of states of anxiety in the pathogenesis of primary glaucoma, Mark J Schoenberg, Discussion by Smith Elv Jelliffe, Joshua Rosett, F Fremont-Smith

APRIL 18—*Medicine* Executive session—Nomination of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] Acute changes in the early lesions of pulmonary tuberculosis, Wm H Stearns, ¶B Service of Bellevue Hospital (by invitation), Discussion by J Burns Amberson, b] A practical method of visualizing the chambers of the heart and the thoracic blood vessels in man, George P Robb, Department of Therapeutics, N Y U College of Medicine (by invitation), Israel Steinberg, 3rd Medical Division, Bellevue Hospital (by invitation), Discussion by Arthur C deGraff, c] Coarctation of the aorta with mycotic aneurysm in a child of ten years, Gertrude H B Nicolson (by invitation), Discussion by F Elmer Johnson

APRIL 19—*Genito-Urinary Surgery* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Paper of the evening—The treatment of bladder pain—Moving picture demonstration, Carlisle F Schroeder, Detroit, Michigan (by invitation), Discussion by John H Morrissey, Fred McClellan (by invitation), Simon A Beisler ¶ General discussion

APRIL 19—*Otolaryngology* Executive session—a] Reading of the minutes, b] Nominating of Section Officers and one member of Advisory Committee ¶ Papers of the evening—Acute contagious diseases—ear, nose and throat complications—a] Otitis, Alfred Schattner (by invitation), b] Upper respiratory, Arthur Wilson, c] Pneumothorax and emphysema—Intern slides, Morris L Stern

(by invitation), d] Lower respiratory, Jesse Bullowa, e] Poliomyelitis, Philip Stimson, Discussion by Harry Neffson, Wallace Hamilton, Vera V Dolgopol

APRIL 21—*Orthopedic Surgery* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Presentation of case—Cases illustrating first paper of the evening, E Arnheim ¶ Papers of the evening—a] A study of scoliosis following empyema, based on a study of all empyema cases admitted to the wards of the Mount Sinai Hospital from 1932 to 1936, inclusive, Seth Selig, E Arnheim, Discussion by Harold Neuhof, b] Motion picture illustrating internal rotation brace treatment of early coxa anteverta, Henry Milch, c] (1) Motion picture illustrating results in the use of the angle plate, (2) Lantern slides of the Hawley table in the treatment of fractures of the lumbo-dorsal and cervical spine, George W Hawley (by invitation), Ralph D Padula (by invitation), d] Osteomyelitis—acute and chronic (comparison of the end results of cases treated postoperatively with Dakin's solution, Orr method or bacteriophage), Discussion by Robert L Preston, Fred H Albee, Mather Cleveland General discussion

APRIL 25—*Obstetrics and Gynecology* Executive session—Nomination of Section Officers and one member of Advisory Committee ¶ Presentation of case—Congenital absence of vagina—operation, Milton Bodenheimer ¶ Papers of the evening—a] Obstetrics in a general hospital (10,000 cases at the Bronx Hospital), J I Kushner (by invitation), Discussion by Hervey Williamson, b] Roentgenology An aid in obstetric diagnosis and choice of treatment, Julius Jarcho, Discussion by Arthur S Unger, William E Caldwell, Alfred M Hellman ¶ General discussion

APRIL 28—*Special meeting of the section of Dermatology and Syphilology* The second special meeting of a symposium on syphilis was held at the Academy There was inspection of cases from 7 30 to

9 00 o'clock, after which, a discussion open to all practitioners followed ¶ Cases of the following were presented Cardiovascular syphilis, cerebrospinal syphilis, neurosyphilis, visceral syphilis, eye syphilis

MAY 2—*Dermatology and Syphilology* Executive session — Election of Section Officers and member of Advisory Committee For Chairman, Elias W Abramowitz, for Secretary, Lewis B Robinson, for member of Advisory Committee, Leo Spiegel ¶ Presentation of cases— a] Beth Israel Hospital, b] Sea View Hospital, c] Miscellaneous cases ¶ General Discussion

MAY 2—*Combined Meeting, Neurology and Psychiatry and the New York Neurological Society* Papers of the evening— a] Treatment of a case of ulcerative colitis associated with hysterical depression, George E Daniels (by invitation), Discussion by Clarence Oberndorf, C V Burt (by invitation), b] Developments in the psychoanalytic conception and treatment of the neuroses, Sandor Rado (by invitation), Discussion by George E Daniels (by invitation), David M Levy (by invitation), Smith E Jelliffe, c] Psychiatric study of some miraculous cures at Lourdes, Smiley Blanton (by invitation), Discussion by Abraham A Brill, Carl Binger (by invitation), Smith E Jelliffe ¶ Executive session Election of Section Officers and member of Advisory Committee For Chairman, Lewis D Stevenson, for Secretary, Samuel Brock, for member of Advisory Committee, Morris Grossman

MAY 3—*Otolaryngology* ¶ Executive session a] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee For Chairman, Jacob L Mabin, for Secretary, Page Northington, for member of Advisory Committee, Francis W White ¶ Presentation of cases—a] Primary carcinoma of middle ear and mastoid recovery after operation and radiation Postoperative results of endaural modified radical mastoidectomy, Clarence H Smith b] Mastoiditis masked by the administra-

tion of sulfanilamide, Samuel Rosen, c] Otitic hydrocephalus, Harry Rosenwasser, d] Lateral sinus thrombosis—unusual course, Louis Hubert ¶ Case Reports—a] Squamous cell carcinoma of the nasopharynx and the petrous pyramid, Joseph G Druss, b] Needle in aorta (Lantern Slides), Bilateral empyema (Leptothrix), David H Jones ¶ Papers of the evening—a] Experimental evidence of gonadotropic hormone in nasal and sinus mucous membranes, A A Eggston, b] The nasogenital and urogenital relationships, Hector Mortimer, Montreal (by invitation)

MAY 5—*Surgery* Executive session—1] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee For Chairman, J William Hinton, for Secretary, Grant P Pennoyer, for member of Advisory Committee, Frank L Melenev ¶ Presentation of cases—a] 1 Lobectomy for multiple chronic lung abscesses 2 Total chronic empyema, broncho-pleural fistulae, multiple stage Schede thoracoplasty, Alexander E W Ada, Discussion by John V Bohrer, b] Two cases illustrating pneumonotomy for putrid abscess of the lung, Harold Neuhoef, Discussion by Arthur S W Louroft ¶ Papers of the evening—a] Surgical therapy in pulmonary tuberculosis, Louis R Davidson, Discussion by Howard Lihenthal, b] Non-tuberculous pulmonary suppuration, Carl Eggers, Discussion by Girard Oberender, c] Closure of the large empyema cavities, Frank B Berry, Discussion by Richmond Moore (by invitation) ¶ General discussion

MAY 10—*Historical and Cultural Medicine* Executive session—a] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee For Chairman, Louis Casamajor, for Secretary, Ramsay Spillman, for member of Advisory Committee, Howard Reid Craig ¶ Papers of the evening—1] Medicine in Utopia, Herbert Silvette,

University of Virginia (by invitation), Discussion by Ramsay Spillman, b] The curious career of Typhoid Mary, George Albert Soper (by invitation), Discussion by F Warner Bishop ¶ General discussion

MAY 11—*Pediatrics* Case demonstrations Executive session—Election of Section Officers and member of Advisory Committee For Chairman, Rustin McIntosh, for Secretary, Leslie O Ashton, for member of Advisory Committee, Philip M Stimson ¶ Presentation of single case reports—a] Willard Parker Hospital, Pertussis and pyloric stenosis (unoperative), Frank S Cross (by invitation), b] Babies Hospital, Progressive myositis ossificans, Donovan I McCune (by invitation), c] St Luke's Hospital, A case of influenza meningitis with recovery, Frederick H Wilke, d] Lenox Hill Hospital, A case of precocious sexual development in a male child, aged three and a half years, Frederick Castrovinski (by invitation), e] New York Post-Graduate Hospital, Vaccinia with interesting features, Irving Posner (by invitation), f] Metropolitan Hospital, Pneumococcus meningitis treated with sulfapyridine, Irving Weinstock (by invitation), g] Roosevelt Hospital, Case of non-pneumococcal pneumonia simulating typhoid fever, John Landon, h] Polyclinic Hospital, Rupture of the stomach in the new born, Abraham Tow, i] The Mount Sinai Hospital, Addison's disease in a boy of twelve, George J Girardes (by invitation), j] New York Hospital, Purulent arthritis in an infant, John Washington (by invitation)

MAY 15—*Ophthalmology* Instructional Hour—Allergic manifestations of the eye W C Spain ¶ Slit lamp demonstration—Milton L Berliner, Wendell L Hughes, Girolamo Bonaccolto, Gordon M Bruce ¶ Executive session—1] Reading of the minutes (8 30), b] Election of Section Officers and member of Advisory Committee For Chairman, David H Webster, for Secretary, Robert K



thermia, Louis Lichtenstein, Hospital for Joint Diseases (20 minutes), b] Hemostatic mechanisms as a cause of visceral lesions, Abraham Penner, Alice Bernheim, Mount Sinai Hospital (30 minutes) ¶ Executive session

MARCH 20—*New York Roentgen Society (in affiliation with The New York Academy of Medicine)* Papers of the evening— a] The treatment of ovarian carcinoma, William Harris, Robert I Walter (by invitation), Arnold L Bachman (by invitation), b] Post-irradiation changes in the lung, a clinical, roentgenological and pathological study, with emphasis on the late and terminal stages, Jacob R Freid, Henry Goldberg (by invitation) ¶ Discussion by Howard C Taylor, Jr (by invitation), Harriet C McIntosh ¶ Executive session

MARCH 23—*New York Pathological Society (in affiliation with The New York Academy of Medicine)* ¶ Case reports— a] Multiple plasmoma of the small and large intestine, Chester R Brown (by invitation) and Amour F Liber (by invitation), Lincoln Hospital, b] Post-traumatic (but not post-fractural) rarefaction of long bones, Henry L Jaffe, Hospital for Joint Diseases ¶ Papers of the evening— a] Spontaneous tumors of rabbits and their transplantation in the same and in alien species, Harry S N Greene (by invitation), Rockefeller Institute for Medical Research, Princeton, New Jersey, b] Sarcomas of the trachea, Tobias Weinberg, Mount Sinai Hospital ¶ Executive session

APRIL 17—*New York Roentgen Society (in affiliation with The New York Academy of Medicine)* Papers of the evening— a] The roentgen diagnosis of myocardial infarction, (1) Theroentgenkymographic findings, Marcy L Sussman, (2) Correlation of the clinical course and electrocardiographic findings with the roentgenkymographic findings, Simon Dack (by invitation), (3) The fluoroscopic diagnosis, Arthur M Master (by invitation), Discussion opened by Bernard S Oppenheimer (by invitation), b] X-ray visualization of soft structures of preg-

nancy, William Snow, Discussion opened by Ross Golden ¶ Executive session

APRIL 27—*New York Pathological Society (in affiliation with The New York Academy of Medicine)* Program arranged by the New York Post-Graduate Hospital Case reports— a] Xeroderma pigmentosum, D S D Jessup, b] Acquired right-sided parasternal diaphragmatic hernia, R A Colmers (by invitation), c] Pulmonary atresia and "tetralogy of Fallot", L H Meeker ¶ Papers of the evening— a] Prolonged hyperpyrexia with necropsy, W J MacNeal, H H Ritter (by invitation), S M Rabson, b] Experimental endocarditis due to infection with streptococcus viridans, M Wasseen (by invitation), M J Spence (by invitation), W J MacNeal ¶ Executive session

MAY 15—*New York Roentgen Society (in affiliation with The New York Academy of Medicine)* Papers of the evening— a] Physical factors of low voltage short distance Roentgen ray therapy (contact therapy), Carl B Braestrup (by invitation), Irving H Blatz (by invitation), b] Recent experiences with low voltage short distance Roentgen therapy (contact therapy), William Harris ¶ General discussion opened by L D Marinelli (by invitation), George T Puck ¶ Executive session— a] Election of officers, b] General business

MAY 25—*New York Pathological Society (in affiliation with The New York Academy of Medicine)* Case reports— a] A case of true hermaphroditism, Milton Helpert, Medical Examiner's Office (10 min), b] Rhabdomyoma of the uterus, N C Foot, New York Hospital (10 min) ¶ Papers of the evening— a] Perineurial fibroblastoma, rather than Schwannoma A histological study, I M Parlov, Jewish Hospital of Brooklyn (30 min), b] Absorption and utilization of Vitamin K Studies in experimental animals and in man, Robert A Moore, William DeW Andrus, Jere Lord, Isabel Bittinger, Cornell University Medical College (30 min) ¶ Executive session

## DEATHS OF FELLOWS

**ALOFSIN, LOUIS MARK** 448 West 34 Street, New York City, born in Russia, October 22, 1883, died in New York City, May 31, 1939, graduated in medicine from the Long Island College Hospital in 1907, elected a Fellow of the Academy November 6, 1930

Dr Alofsin was a Fellow of the American Medical Association, a member of the Alumni of the French Hospital and a member of the County and State Medical Societies

**FALKNER, EBENEZER ROSS** 101 East 58 Street, New York City, born in Glenholme, Nova Scotia, January 28, 1876, died in New York City, May 25, 1939, received the degree of Bachelor of Arts from Dalhousie University, Halifax, Canada in 1897 and graduated in medicine from that University in 1901 elected a Fellow of the Academy, November 3, 1910

Dr Faulkner had been surgical director of the Manhattan Eye, Ear and Throat Hospital and consultant to the French Hospital, Yonkers General Hospital, and St Joseph's Hospital of Far Rockaway. For several years he was professor of laryngology and rhinology at the Polyclinic Hospital

Dr Faulkner was a Fellow of the Royal College of Surgeons of England, a Fellow of the American Medical Association, a diplomate of the American Board of Otolaryngology and a member of the American Academy of Ophthalmology and Otolaryngology, the New York Otolaryngological Society, the American Laryngological Association, the American Laryngological, Rhinological and Otological Association, and the County and State Medical Societies

**LAMBERT, ALEXANDER** 43 East 72 Street, New York City, born in New York City, December 15, 1861, died in New York City, May 9, 1939, received the degrees of A.B. in 1884 and Ph.D. in 1885 from Yale University, graduated in medicine from the College of Physicians and Surgeons, New York, in

1888, elected a Fellow of the Academy May 2, 1893

Dr Lambert was professor of clinical medicine at Cornell University Medical College, 1898-1931, attending physician to Bellevue Hospital, 1894-1933, and assistant bacteriologist to New York City Department of Health, 1894-1901. It was largely on Dr Lambert's initiative that the Doctors Hospital was founded and he was president of the medical board of that institution at the time of his death

Dr Lambert was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and its president in 1919, a member of the Association of American Physicians, and a member and former president of the State Medical Society

Dr Lambert was a Colonel in the Medical Auxiliary Corps of the U. S. Army, having served in France from 1917 until the end of the War. While in France he headed the Medical Division of the American Red Cross

In the biography of General Gorgas by Marie D. Gorgas and Burton J. Hendrick, Dr Lambert is credited with saving the official head of Dr. William C. Gorgas as director of the sanitary work during the building of the Panama Canal

**STUBENBORD, WILLIAM** born in Gernersheim, Bavaria, Germany, September 29, 1851, died in New York City, May 23, 1939, graduated in medicine from New York University Medical College in 1879, elected a Fellow of the Academy March 3, 1887. Dr Stubenbord was a member of the County and State Medical Societies

**WARD, GEORGE HAROLD** 240 Engle Street, Englewood, New Jersey, born in Nipawee, Canada, August 16, 1879, died in Blairstown, New Jersey, May 30, 1939, graduated in medicine from Queen's University, Kingston, Ontario, Canada in 1903, elected a Fellow of the Academy November 3, 1910

Dr Ward was chief of the eye, ear, nose and throat division of the Englewood, Holy Name and Teaneck Hospitals and consultant to the Njack and Rockland County Hospitals. He was a member of the State and County Medical Societies





## ANNOUNCEMENT

### THE ROBERT LIVINGSTON SEAMAN FUND

The New York Academy of Medicine announces the establishment of "The Robert Livingston Seaman Fund for the furtherance of research in bacteriology and sanitary science," with six hundred dollars available for assignment in 1939. This fund has been made possible by the terms of the will of the late Dr. Robert Livingston Seaman and will be administered by a committee of the Academy of Medicine under the following conditions and regulations:

1. The committee will receive applications from either institutions or individuals during the summer and up to September 15, 1939. Communications should be addressed to Dr. Wilson G. Smillie, Chairman, 2 East 103 Street, New York City.
2. The fund will be expended only in grants in aid for investigation or scholarships for research in bacteriology or sanitary science. The expenditures may be made for:
  - A. Securing of technical help
  - B. Aid in publishing original work
  - C. The purchase of necessary books or apparatus

BULLETIN OF THE NEW YORK  
ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED  
IN THEIR CONTRIBUTIONS

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1939

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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



AUGUST 1939

OBSERVATIONS ON THE PATHOLOGY OF  
RICKETS WITH PARTICULAR REFERENCE  
TO THE CHANGES AT THE CARTILAGE-  
SHAFT JUNCTIONS OF THE  
GROWING BONES

*Harvey Lecture, February 16, 1939*

EDWARDS A. PARK

HISTORICAL

ALTHOUGH rickets was first clearly recognized and described by Glisson<sup>1</sup> in 1650, knowledge concerning the disease remained almost stationary for more than 200 years. It was the monumental contribution to the pathology of rickets by Pommer<sup>2</sup> in 1885 which broke the spell. It laid the foundations of present knowledge concerning the pathological changes and gave correct interpretations of the main features with the exception of the cause of the accumulation of the proliferative cartilage. Since the appearance of Pommer's work, the most important contribution has been that of Schmorl<sup>3</sup> (1909), although his service was to supply sound judgments and points of view rather than new observations or conceptions. A distinct advance followed the experimental production of rickets in animals by Sherman and Pappenheimer<sup>4</sup> (1921) and McCollum, Simmonds, Shipley and Park<sup>5</sup> (1921). The splendid

recent studies by Dodds and Cameron,<sup>6</sup> which have yielded greatly needed precise information, were performed on the rat. Discoveries in other fields have had influence in the interpretation of the pathological changes. We refer in particular to the work of Iversen and Lenstrup<sup>7</sup> (1920), and Howland and Kramer<sup>8</sup> (1921), which disclosed the characteristic deficit in the inorganic phosphorus of the blood and to the work of Holt, LaMer and Chown,<sup>9</sup> Shear and Kramer,<sup>10</sup> Logan and Taylor<sup>11</sup> and others, on the nature of the deposition of mineral matter in bone and the principles involved. The discovery that rickets is a deficiency disease depending on a lack of vitamin D (Mellanby,<sup>12</sup> McCollum, Simmonds, Becker and Shipley<sup>13</sup>) is the most fundamental of all, but it has not contributed directly to the elucidation of the pathology.

### THE FUNDAMENTAL CHEMICAL DISTURBANCE

The pathological changes depend on and hence follow a change in the chemical structure of the blood. Most commonly the inorganic phosphorus has fallen to a subnormal concentration, less often the calcium, occasionally both. The result is a depression in the Solubility Product (SP) which governs the precipitation of calcium phosphate from the blood (lymph) into the cartilage and bone.\* When the SP falls below a certain critical value, lime salt deposition in bone and cartilage becomes irregular and, if the value is low enough, deposition stops altogether. The failure in lime salt deposition is responsible for the weakness of the bones. This, in turn, results in the development of the well known deformities of the disease and at the same time is the cause of almost, if not all, the histological changes. The first demonstrable pathological change in rickets is the failure of lime salt deposition in the proliferative cartilage of the epiphysis and in newly forming bone.

### THE CHANGES IN BONE\*\*

If the rachitic process is of sufficient severity, bone is formed without lime salts. Bone free from lime salts is known as osteoid, i. e., osteoid is the organic part of bone without the inorganic. Since in endochondral

\* We speak of the SP as a symbol, standing for the general chemical conditions in the blood (lymph) which determine the deposition of calcium phosphate. We are aware not only that its chemical expression is uncertain but also that its postulation is not entirely justifiable at the present time.

\*\* In all descriptions the bone is conceived of as standing on end with the epiphysis upwards. Hema-  
toxylin and eosin stains are referred to throughout.

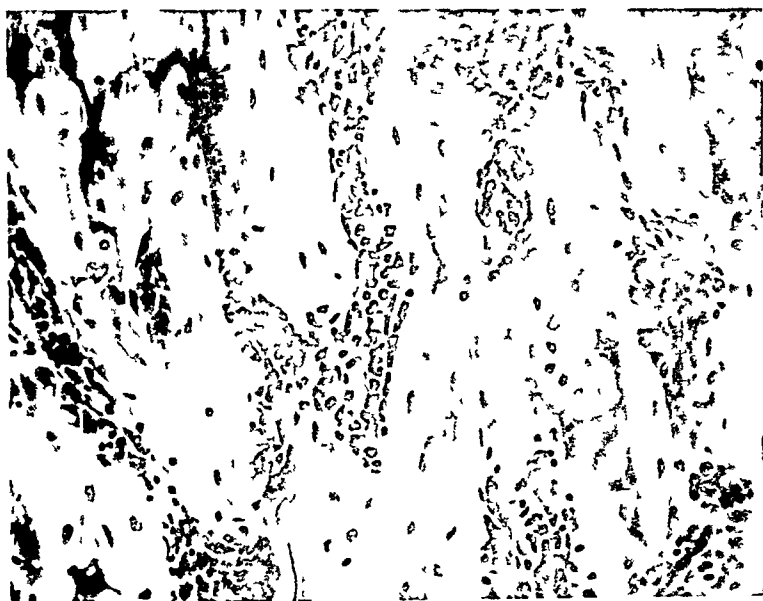


Fig 1—Photomicrograph (high power view) from a microscopic section, taken from upper end of tibia of the rat

The bone marrow lies between the trabeculae The black areas in the trabeculae represent the cores of the original framework of calcified matrix substance of the cartilage on which the osteoblasts settled and formed bone The gray represent the lime salt containing part of the trabeculae formed before the rickets began, the white borders, the osteoid formed under the influence of the rickets

ossification new bone forms always on a nucleus or core of old bone or of matrix framework of the cartilage, osteoid always makes its appearance as a surface covering of the trabeculae or matrix framework (Fig 1) It stains differently from bone that contains lime salts and in that way can be differentiated from the latter In histological sections, which of course represent single planes, the osteoid coatings always appear as borders (staining pink with eosin) to the lime salt containing trabeculae (staining bluish gray with hematoxylin) or to the matrix substance of the cartilage (which, if calcified, stains a deep blue)

Osteoid is not peculiar to rickets, it develops in the course of normal growth, for, when new bone forms in the healthy individual, it is entirely devoid of lime salts The lime salts deposit in it later Thus, under normal conditions, one finds trabeculae with borders of osteoid In the most rapidly growing bones, those of young prematurely born infants,

osteoid borders are numerous and of considerable breadth. In contrast, in infants suffering from wasting diseases which interfere with osteoblastic activity, as they very probably do with cellular activity in general, osteoid borders may not be found at all, or, if found, are very thin. In the older child in whom growth has waned and in the adult in whom growth takes place only to the extent necessary to counterbalance destruction, osteoid is entirely lacking or at best poorly developed. There is, therefore, a wide variation in the amount and thickness of osteoid coverings under normal conditions, explicable on the basis of variations in the rate of bone growth.

The difference in the osteoid in rickets and the normal state is entirely one of degree. In rickets the osteoid borders are both wider and more generally distributed than normal. The histologist, searching for rickets, scans the shaft, to see if osteoid is in excess. If the osteoid borders appear abnormally broad and abundant, he feels confident that the disease exists.

Schmorl<sup>3</sup> regarded excessive amounts of osteoid in the shaft essential for the diagnosis of rickets and considered it the earliest as well as the most reliable sign of the disease. We are certain, however, that an excess of osteoid is not an invariable characteristic, for we have repeatedly found instances in which it was absent in infants having scurvy, tuberculosis or other wasting diseases, although indubitable evidences of rickets were present at the cartilage-shaft junctions. Proliferation of the cells in the cartilage is responsible for growth of the bone in length, osteoblastic activity in the shaft is responsible for growth of the trabeculae and cortex in thickness. The two processes are, to an extent at least, independent. When osteoblastic activity stops, while growth activity in the cartilage continues, the formation of osteoid borders in the cancellous tissue of the shaft and in the cortex ceases altogether, but the abnormal developments in the cartilage continue. It is wrong, therefore, to conclude that the presence of osteoid in the shaft is absolutely necessary for the diagnosis of rickets, although we admit a certain sense of insecurity if it is not present. Sometimes, in states of malnutrition, when osteoid is almost entirely absent, one can find here and there bits of it having such thickness as to fix the presence of rickets. Sometimes, the osteoid borders are not broader than normal but are so numerous as to establish the rachitic state. Schmorl<sup>3</sup> pointed out that osteoid is especially developed in those parts of the skeleton which are

particularly subject to mechanical strain and hence to rapid growth. In general, however, the distribution of osteoid is fairly even. At the upper end of the ulna, for example, where cartilaginous growth is so slow that rickets may not show itself at all at the cartilage-shaft junction, the osteoid borders in the cancellous tissue of the shaft will be found as well developed as at the ends of the fast growing ribs. Oftentimes, osteoid is found in the cortex, when it is practically absent in the cancellous tissue. One must be careful, however, in making the diagnosis of rickets from the presence of osteoid in the cortex alone, because in rapidly growing bones, in particular those of prematurely born infants, the osteoid borders are apt to be wide in that location. In some cases of rickets we have found the widest osteoid borders in the trabeculae close under the cartilage, in others at a distance in the shaft. In osteomalacia (the rickets of the adult) the only characteristic sign of the disease is the presence of abnormal amounts of osteoid in the shaft and in rickets in the older child its presence may be the sole evidence of the disease, since growth of the cartilage is occurring too slowly for rickets to show at the cartilage-shaft junction. At the ends of the long bones where cartilaginous growth is very slow even in very young infants, the disease must be recognized by the presence of excess osteoid.

In summary we can say that the presence of osteoid in excess is a cardinal sign of rickets and is pathognomonic of the disease. It is the only sign of the disease in osteomalacia and may be the sole sign in the older child. In the prematurely born infant it is often difficult to be certain that an excessive development of osteoid may not be the result of unusual growth activity. The absence of osteoid does not mean that rickets cannot be present.

*Does halisteresis occur in rickets?* The question has been much debated whether halisteresis ἅλς [salt] and στέρησις [deprivation]—the withdrawal of lime salts from the organic matrix—occurs in rickets. It is of paramount importance to the histologist to know whether to regard osteoid borders as invariably indicative of formation without lime salts or whether they may represent old bone out of which the lime salts have been dissolved. Such distinguished students of rickets as von Recklinghausen<sup>14</sup> and M. B. Schmidt<sup>15</sup> have held that halisteresis occurred in rickets and osteomalacia, whereas others, notably Pommer<sup>2</sup> and Schmorl,<sup>3</sup> have denied the possibility. The more we have studied rachitic bone, the more we have been convinced that halisteresis does



not take place. Apparently Nature's method of obtaining calcium from bone is not to dissolve it, leaving the organic matrix behind, but to break down the organic matrix at the same time that the mineral content is released. Chemists annoy histologists when they speak of decalcification of bone, as if bone were not a living tissue but were composed entirely of inorganic material subject to the laws of the test tube. Even if lime salts are dissolved by some chemical agent, perhaps an acid elaborated by the bone cells, it is necessary to think of the organic matrix, in which the lime salts are imbedded, as being dissolved or disintegrated at the same time. Schmorl<sup>3</sup> made the observation that in areas in which destruction of bone was taking place the leukocytes contained granules of calcified matter.

*The distribution of osteoid and its probable significance.* Osteoid is not spread evenly over the surfaces of the trabeculae like the chocolate coating of a candy, except possibly over limited areas in some places in the cortex. On the contrary it appears on the surfaces of the trabeculae only here and there. A remarkable feature about osteoid formation in rickets is the complete irregularity of its distribution. Often osteoid borders are present on both sides of a trabecula. As commonly, an osteoid border is found on one side, perhaps of a very thin trabecula, and an area of destruction on the other side, or areas of osteoid formation and of destruction lie side by side (Fig. 2). The only possible explanation of the close intermingling of new bone formation (so easily recognized in rickets because the newly formed bone is osteoid) and old bone destruction is that mechanical conditions are the determining factors. The common occurrence of osteoid on one side of a trabecula and a destructive process on the opposite side is exactly what would be expected, if pressure stimulated new bone formation and tension exerted no influence at all or perhaps was actually destructive. The occurrence of osteoid and areas of bone destruction side by side might also be anticipated, on that hypothesis, if the sinuosity of the trabeculae is taken into consideration. The theory that pressure causes new bone formation and tension is without effect has already been advanced by Jansen.<sup>16</sup>

*Is bone destruction increased?* The reason that the bones become so weak in rickets is that old bone, i. e., the old lime salt containing bone antedating the advent of rickets, undergoes surface disintegration while the new bone formed, being osteoid, does not possess strength on account of its lack of lime salts. The reason that rachitic bone appears

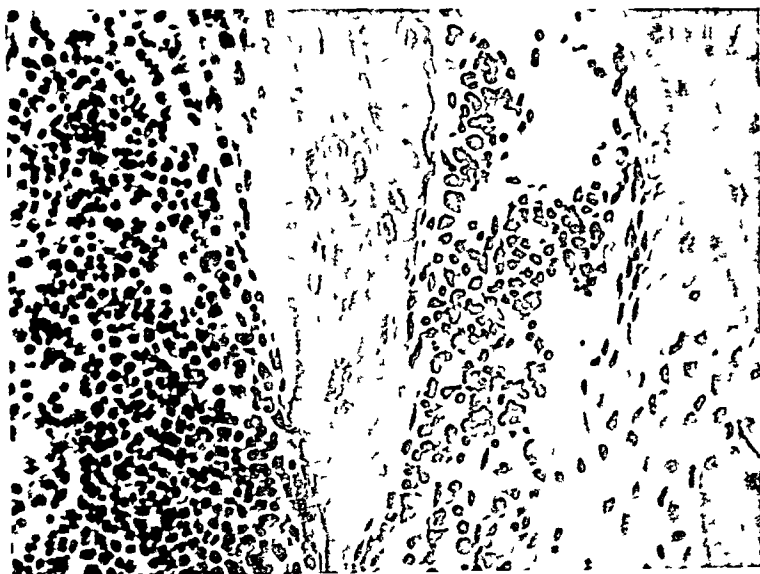


Fig 2—Photomicrograph (high power view) from a microscopic section, taken from rib of A J (No 948) aged four months

In the center is a trabecula. On the left hand side of it an osteoid border becomes thinner, as it descends, and finally stops altogether. Just below where it stops is an area of destruction. Thus on the left side one finds abrupt transition from formation to destruction. On the opposite (right) side the reverse condition is present, namely, bone destruction above, osteoid formation below. The illustration is presented, in order to show how closely new bone formation, which can be traced so beautifully in rickets, and old bone destruction are intermingled.

so rarefied in the x-ray film is because the old lime salt containing bone is reduced whereas the newly formed bone casts little shadow.

The question has been debated whether in rickets destruction of old lime salt containing bone is increased. The histologist is not the one capable of giving final judgment. All that he is able to contribute is the *impression* that the areas of resorption, as seen under the microscope, are or are not more numerous than he would expect under normal conditions. The measurement of the density of rachitic bones by means of the x-ray indicates that the destruction of lime salt containing bone must have been extreme but does not exclude prolonged action of normal forces. In metabolism studies in rickets, however, the balance of calcium is rarely negative. From this fact one can infer that the destruc-

tion of old bone can only rarely be of extreme degree. In hyperparathyroidism, in which we know that bone destruction is greatly increased, the calcium balance is regularly negative (Bauer, Albright and Aub<sup>17</sup>) and the urinary excretion of calcium is increased. In rickets the urinary excretion is unaffected or becomes diminished (Orr, Holt, Wilkins and Boone<sup>18</sup>). The loss is from the bowel, due almost entirely to failure in absorption (Telfer<sup>19</sup> and Nicolaysen<sup>20</sup>). Hamilton and Highman<sup>21</sup> have shown that in the rabbit in which rickets has been produced by a low phosphorus diet the actual quantity of calcium contained in a given bone becomes reduced, in spite of continued growth in length. We can conclude that usually in human rickets destruction of bone cannot be greatly increased but undoubtedly may be increased in the severest developments of the disease. However, such factors as the inactivity resulting from weakness or general malnutrition may take part in the process.

#### CHANGES AT THE CARTILAGE-SHAFT JUNCTION

Before we take up the changes at the cartilage-shaft junction we must make clear that rickets occurs in all degrees of severity. It may be so mild as to be scarcely distinguishable by any means or so severe as to threaten the integrity of the skeleton. Chronic rickets with lime salt depositions occurring sporadically is very common, it may last for years. A description of the lesions at the cartilage-shaft junctions in severe forms of the disease would not fit the mild or the chronic, although the underlying disturbance remains the same in all. We must also bring out the fact that rickets affects the growing ends of bones in different degrees according to the rate of growth of the cartilage. For example, the slow growing upper end of the ulna will show little evidence of the disease at a time when the rapidly growing anterior end of the eighth rib shows most pronounced effects. A description of the former would not apply to the latter, although the principles in operation are the same.

*The earliest manifestations* The first signal of rickets at the cartilage-shaft junction is failure in the usual lime salt deposition in the layer of cartilage close to the shaft. Defective calcification at the cartilage-shaft border and osteoid formation in the shaft develop together. They are the first and the essential manifestations in the skeleton. As the result of the loss of the normal support furnished by the lime salts the tissues bordering on the cartilage-shaft junction give way and are pressed

together. Compression is not, however, a constant manifestation either in all individuals or in all bones. The circulation at the cartilage-shaft border becomes disarranged, the orderly invasion stops. The proliferative cartilage begins to increase in amount. Its swelling can sometimes be actually demonstrated. Presently a disorderly invasion commences. It may, then, be observed that in certain places along the cartilage-shaft border, where the cartilage is touched by the blood vessels curious changes develop in it.

Considering the matter from the practical viewpoint, the pathologist searches to see if there are small gaps in calcification, and if in places the deposition is of an abnormally light or fragmentary character, or if it extends less than the wonted distance into the substance of the cartilage, also, if the capillaries are abreast of its furthest outposts or if some have even begun to enter the uncalcified cartilage beyond. He inspects the advance fringe of calcified matrix framework to learn if the spicules are bent or broken, and examines the cartilage cells closest to the shaft for evidences of compression or displacement. He tries to estimate if the fully developed cartilage cells are in excess. Finally he looks at the cortex and cancellous bone with the greatest care, in order to form an opinion whether the osteoid is in excess of normal.

Wolbach<sup>22</sup> states "The first histological evidence of rickets is the absence in whole or in part of the layer of clear cells and the consequent absence of ingrowth of capillaries." Schmorl<sup>13</sup> regards connective tissue formations immediately under the cartilage as one of the earliest signs.

We shall now describe the changes which mark the beginning of rickets, as we see them, and shall trace their development, trying to explain why they occur, even though essential facts are lacking.

*The disturbance in calcification.* By killing young rats in succession it is possible to trace the disturbance in calcification at the cartilage-shaft junction. Within twenty-four hours after the substitution of the Steenbock-Black rickets-producing diet (Steenbock and Black<sup>23</sup>) it is manifest, for the fringe of the framework of calcified matrix extending into the cartilage between the cells has already given way. According to Dodds and Cameron<sup>6</sup> deposition first fails in the thinner parts of the matrix framework of the cartilage. In the more massive parts it continues but occurs most constantly at the intersections. It gradually diminishes and at the end of two or three weeks ceases altogether. The defects in calcification are very small at first.

The disturbance in lime salt deposition at the cartilage-shaft junction in the infant develops in a similar manner. In the fast growing ribs of the young infant one finds that here and there the spicules of calcified matrix framework are thin and in spots two to four or more cartilage cells in diameter, the lime salts have failed to precipitate altogether or have fallen in thin, fragmentary fashion. Under normal conditions, lime salts do not deposit in the thin matrix partitions separating the cartilage cell columns of the bundles from each other but they do deposit in the more massive main partitions which lie between individual columns and bundles of columns. It is common to find that calcification of a main partition may be lacking here and there or that it has occurred only along the border of the partition where the latter touches the cartilage cells, or that the deposition is represented only by fragments, in histological preparations, at least, appearing to be completely disconnected from the rest of the network. The calcification may extend only a short distance into the proliferative cartilage. When one finds this, he is at a loss to know whether it had never extended the normal distance, or whether it had stopped advancing and the marrow vessels had caught up with it. The spots of defective calcification are only a few cells wide and are irregularly scattered exactly as in the rat.

In bones which are growing slowly no defects in lime salt deposition may be apparent for some little time after rickets shows itself plainly elsewhere. They develop gradually. They may be small, when first noticed, but are often fairly large. Underneath them it is common to observe distended blood vessels.

If the rickets continues and invasion of the cartilage occurs, the blood vessels keep carrying away the lime salt deposits and the defects become wider.

It is not possible to discover by histological methods any change in the cartilage which fails to calcify in order to account for the failure. We shall return to the subject of calcification further on.

*Compression* As in the case of calcification, development of compression at the cartilage-shaft junction can be readily followed in the rat but not in the human being. At the upper end of the tibia of the rat it is already well developed at the end of twenty-four hours on the Steenbock-Black rickets-producing diet. The compression involves the lowermost cells of the proliferative cartilage and the interdigitating fringe of calcified matrix framework. Both the capsules which are as yet unopened

by capillaries and those which have just been opened are affected. The collapse of the cell capsules may be partial or complete. If the collapse is incomplete, the spicules of calcified matrix substance are bent or buckled or may be fractured and the cell capsules are pressed into a variety of shapes. If the collapse is complete, the unaffected blue staining proliferative cartilage rests against the end of the shaft with the layer of collapsed tissues between. In the severest degrees of compression the intracellular spaces are obliterated and the spicules are flattened out, so that they lie horizontally. They may be impacted into or driven against the soft cartilage. The compression zone is rarely continuous across the cartilage-shaft junction and in the case of the upper end of the tibia, which is the bone we have studied, the peripheral parts remain free. Indeed, in that bone at the anterior end of the cartilage-shaft junction cartilage and shaft often are torn apart. Commonly the compression occurs in spots alternating with uncompressed areas. As the rickets progresses, collapse continues. The tissues which are freshly formed under the rachitic influence keep giving way, so that one finds strata of compressed tissues at higher levels in the shaft. But the original stratum of compression persists and can be readily identified for two or more weeks in the substance of the shaft. From it one can locate the starting point of the rachitic process.

In the human being collapse at the cartilage-shaft junction also occurs very early and may be exactly like that just described in the rat (Fig 3, *a, b, c* and *d*), that is, both the layer of large swollen cartilage cells in contact with the shaft and the fringe of calcified matrix substance, which has extended in between them, are involved. As in the rat, the cell capsules may be partly collapsed, so that the intracellular spaces remain partially open, or they may be completely flattened. The spicules of the fringe may be simply bent to one side or extensively buckled or fractured or flattened so that they lie horizontally. As in the rat, at the extreme periphery compression is not usual. If no lime salt deposition has taken place in the cartilage in contact with the shaft, the cartilage alone is affected in the compression process. In an illustrative specimen in our possession the compression of the under surface of the proliferative cartilage was at least fifteen cells deep. The ends of the trabeculae were driven into the soft cartilage. At the points of impaction the cartilage cells were squeezed flat and had the appearance of fibrous connective tissue with nuclei running horizontally. In the spaces between the trabe-

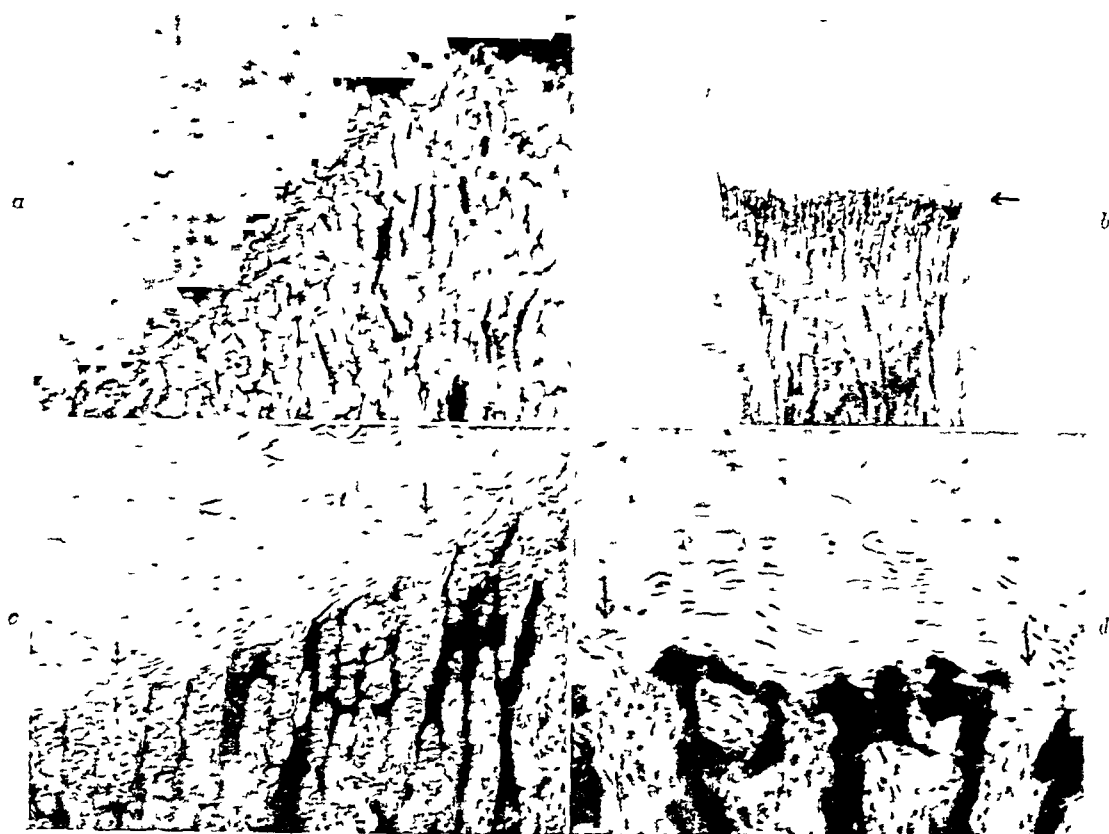


Fig 3

Fig 3—*a* Photomicrograph (low power view) from a microscopic section of the upper end of the tibia of the rat killed twenty-four hours after the substitution of the Stenbock-Black rickets-producing diet for the stock diet.

The picture is presented in order to show that, already, collapse of the fringe of framework of calcified matrix substance has taken place. The crushed fringe embraced not only the cartilage cell capsules which had just been penetrated but also the capsules of the lowermost fully developed cartilage cells which were in process of being attacked.

Fig 3—*b* Photomicrograph (low power view) from a microscopic section of the lower end of the ulna of W. H. (No. 1073) aged two months.

The picture shows the bending and fracture of the fringe of the framework of calcified matrix substance. The condition in this infant corresponds exactly to that just shown in the rat in Fig 3, *a*.

Fig 3—*c* Photomicrograph (low power view) from a microscopic section of the rib of J. R. (No. 1015) aged two months.

The picture shows the compression which is resulting in stratification, of the lowermost cartilage cells, those in contact with the trabecular framework. The ends of the spicules of the trabecular framework are bent and everted to the right. At the left (the point indicated by an arrow) pocket formation has commenced and at the top of the pocket

culae the cartilage bulged downwards into the shaft and had a looser, more nearly normal arrangement. If the rickets continues, the weak tissues forming under its influence keep on giving way from time to time as in the rat. But these collapses are not conspicuous unless lime salts are present to mark the pattern.

Slight degrees of compression are much commoner than the severe ones described. The cartilage capsules next the shaft are oval or show a variety of irregular shapes and often are squeezed out of line, so that the columnar arrangement is gone. Also, as in the rat, the compression areas are scattered and seem to have a special connection with certain trabeculae or trabecular groups.

Collapse at the cartilage-shaft junction, as already pointed out, does not occur universally in rickets. It is a phenomenon, as might be imagined, dependent on the combination of rapid growth, severe rachitic state and pressure. It will not be found at the cartilage-shaft junctions at which growth is very slow. We find it chiefly at the fast growing ends of the long bones in young infants in whom severe rickets has developed suddenly. Compression signs will not be found at the slow growing ends of the bones because their strength is so little impaired. It is remarkable, however, if one examines with great care the entire breadth of the cartilage-shaft junction, in particular the points at which the trabeculae abut on the cartilage, how often slight degrees of compression are present.

The cause of the compression is evident enough. Apparently the extension of the lime salt deposition into the framework of matrix substance of the cartilage is designed not alone to guide the invading capillaries but

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is a fragment of calcified matrix substance. At the point on the right indicated by the arrow a blood vessel has begun to work its way into the cartilage.

Fig 3—d Photomicrograph (high power view) from a microscopic section of the rib of F R (No 165) aged two years.

The picture shows the most extreme compression of the bottom-most part of the proliferative cartilage. The compressed tissue is ten to fifteen cells deep. The lacunar spaces are represented by slits. The advance fringe of the framework of calcified matrix substance has been fractured and bent back with the crushing of the cartilage cells in the general collapse. The reason that the framework does not extend into the substance of the cartilage is because it has been flattened out. Formerly it did extend into the cartilage between the cell columns. At the two points indicated by arrows invasion is commencing. Between these points in the plane of the section vessels are prevented from reaching the under surface of the cartilage as the result of the trauma. Compressed cartilage, such as is exhibited, offers a formidable barrier. The columnar arrangement of the cartilage cells is entirely gone.



also to give support to the large swollen cartilage cells bordering on the shaft. Obviously the capsules of these cells are unable, unsupported, to withstand pressure. It is noteworthy that the compression is limited to the lowermost cells, those in contact with the shaft. The weakening process, therefore, does not seem to be the result of aging but rather of the influence of the approaching marrow elements. If the cartilage cell is viewed as a sort of bladder which, when squeezed, is readily flattened out but is prevented from bursting by the circular fibers in its capsule (Benninghoff,<sup>24</sup>) one can understand the variety of form and displacement. The observation that, except in very severe cases, the compression occurs only in localized areas is most important, for the establishment of barriers at the cartilage-shaft junction has a great influence in determining the irregular invasion of the cartilage which presently will be discussed.

*Elongation of the zone of proliferative cartilage.* All pediatricians know that the increase in length of the clear space between the end of the shaft and the nucleus of ossification of the epiphysis, as seen in the x-ray film, is a sign of rickets. Study with the microscope shows that the tissues composing the clear space are proliferative cartilage and trabeculae composed of osteoid covered cores of uncalcified matrix framework, sometimes containing cartilage cell inclusions (chondro-osteoid trabeculae\*), with blood vessels, marrow and connective tissue cells between. The proliferative cartilage occupies the upper part and is greatly in excess of the normal and in the earlier stages of the disease forms the major part of the transparent tissue. The chondro-osteoid trabeculae naturally are found on the shaft side. They vary in quantity very much, increasing as the rickets becomes older. The excess of proliferative cartilage was thought by Pommer<sup>2</sup> to be due to increased growth. He conceived that the cartilage cells multiplied faster than normal as a result of stimulation from the combined influence of some toxin and increased vascularity. The true cause, namely, failure on the part of the forces of the shaft to invade the proliferative cartilage and to build it over into shaft was clearly recognized by Schmorl,<sup>3</sup> although his pet proof, based on the distance apart of the transversely directed blood vessels, rests on an entirely erroneous conception of the blood supply. The proliferative cartilage increases in amount merely because it accumulates. Incidentally, Jahn<sup>25</sup> and Schmorl and Lossen<sup>26</sup> demonstrated that the proliferative cartilage in

\* We use the term chondro-osteoid trabeculae whether the core substance on which osteoblasts have built is composed of uncalcified cartilaginous matrix framework alone or in addition contains cell inclusions.

the non-rachitic rabbit would increase in mass, if the circulation of the shaft were prevented from reaching it

In the rat the part of the proliferative cartilage responsible for the increased length, is the zone of large, fully developed cells. Dodds and Cameron<sup>6</sup> find that the total length of the proliferative cartilage at the upper end of the tibia in rats fed the Steenbock-Black rickets-producing diet for from three to eight weeks may be increased to fifteen times the normal (Dodds<sup>27</sup>) and that the number of cells in the affected zones vary from eighty-eight to one hundred and forty-five, as compared with a normal of about four. Dodds and Cameron<sup>6</sup> find also that the cells have a decreased vertical diameter, they are shorter (flatter) than normal, a phenomenon attributed to defective formation but perhaps due in part to compression. The topmost zone, that of "reserve cells" and the zone of flat cells below, designated "the zone of flattened cells and cell multiplication" showed essentially no changes except that mitosis appeared to be diminished in the later stages of the disease.

Dodds and Cameron's<sup>6</sup> observations on growth of the tibia of the rat in rickets are interesting. They found that the growth in length was retarded from the beginning but continued for about three weeks, and that it then virtually stopped. They ascribed the retardation and stoppage to two factors, first, the diminution in cell multiplication, and, second, the production of cells having a smaller vertical dimension. In our experiments with the rat the tibia stopped growing and the shaft proper, lengthening by the eleventh day and in some instances even earlier.

In the puppy the zone of proliferative cartilage may become enormously increased and it may also be much increased in the rabbit (Fig 4). That the proliferative cartilage can be in great excess in rickets in the case of the human being is common knowledge. Dodds and Cameron's<sup>6</sup> observations on the rat probably apply to the human being. The increase in the length of the proliferative zone is due to an increase in the number of large fully developed cuboidal cells which are the products of cell multiplication. The zones of cell multiplication are not increased in size. It is also probable that in human rickets multiplication of the cartilage cells becomes retarded. We say this because of the well-known fact that, if rickets persists over a number of years, retardation of growth may become extreme. Dodds and Cameron's<sup>6</sup> observations that in the rachitic rat, cell division in the proliferative cartilage dwindles, is of fundamental importance since it shows actual growth processes are affected.



Fig 4—Photomicrograph (low power view) taken from the microscopic section of the upper end of the tibia of a rabbit in which rickets has been produced

The picture is shown in order to illustrate the great broadening of the proliferative cartilage which occurs in rickets and also the irregularity of the invasion. At the sides blood vessels have extended far into the proliferative cartilage and on the left have advanced almost to the normal limit of penetration. The reason that the central portion of the proliferative cartilage remains essentially intact is that it has been protected by a barrier of crushed tissues composed of both cartilage cells and matrix framework.

*Swelling of the proliferative cartilage* The evidences of swelling of the proliferative cartilage can occasionally be found in the human being at the fast growing bone ends. They consist in a deflection outwards of the spicules in the peripheral part of the fringe of calcified matrix substance, while the more central parts retain their vertical direction. Also, the columns of cartilage cells at the extreme periphery bulge above the junction with the shaft, as if prevented from expanding at the shaft level by their attachment.

*Invasion of the cartilage* As long as lime salt deposition in the proliferative cartilage is preserved, normal invasion continues, that is, individual capillaries continue to attack individual cell columns or column groups. But as soon as it becomes disorderly or stops, the focal type of

invasion of the proliferative cartilage, so characteristic of rickets, sets in. This type of invasion depends on failure in lime salt deposition at the cartilage-shaft junction. It commences much sooner, therefore, in severe than in mild rickets. Indeed, as Dodds and Cameron<sup>6</sup> point out, the normal kind of invasion may be approximated indefinitely, if the rickets is mild enough. In the rat when the Steenbock-Black rickets-producing diet is substituted for the stock ration, irregular penetration appears at the earliest on the fourth day and does not become well developed until the tenth. In contrast, the defect in lime salt deposition and the compression at the cartilage-shaft junction declare themselves within twenty-four hours. A latent period, therefore, is required, for the disturbance in invasion to reach the magnitude necessary for it to become apparent. The same is undoubtedly true in the human being.

In the human being we have found the study of the beginnings of the penetration difficult. Apparently the course is not always the same. If fresh calcium deposition has ceased all along the front, it is common to find that the capillaries have advanced to the level of the furthest deposits and that some are extending out into the cartilage in advance of them. This type of invasion is most commonly seen at the cartilage-shaft junctions of the very rapidly growing bone ends in young infants. Another example of invasion, the one often encountered at the slow growing bone ends, is as follows. At various points in the proliferative cartilage calcification is defective. Beneath the defective areas lie dilated capillaries, often in holes or pockets in the lattice framework. Either the pockets happened to be there or they were created by the blood vessels. In some instances the latter explanation seems probable because a fragment of a spicule of calcified substance protrudes from the cartilage edge or lies free in the pocket (Fig. 5), or because one of the more massive partitions of matrix substance ends at the under surface of the cartilage, as if cut away, instead of being continuous with the lattice formation underneath. The matrix substance of the cartilage in contact with the capillary stains yellow (hematoxylin and eosin preparations) and the loss of power to take the blue color has extended upwards. In some instances this change does not occur. Adhering to the under surface of the yellow cartilage are a few cells of the connective tissue family probably mesenchymal cells accompanying the capillary. These are the premonitory signs. In the next stage the vessel has broken into a lacuna or produced an excavation in one of the more massive arms of the matrix.

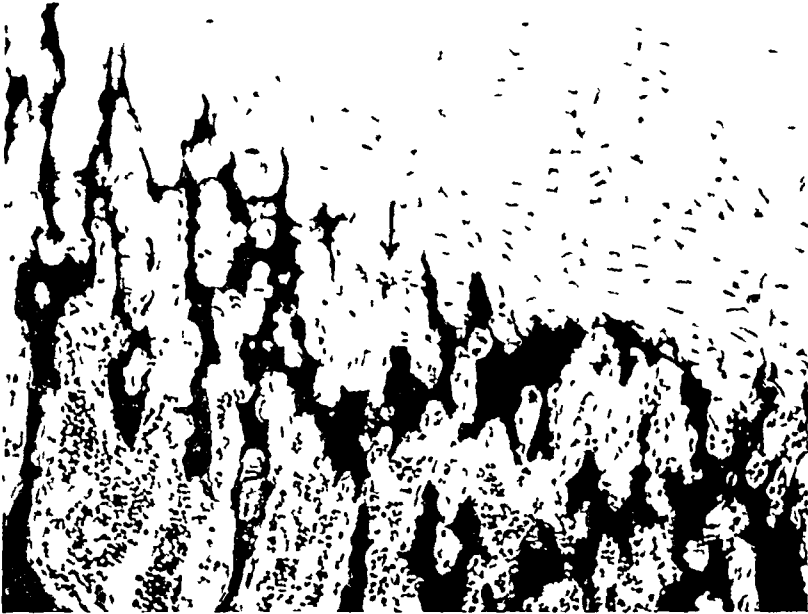


Fig 5—Photomicrograph (low power view) from a microscopic section of the rib of J W (No 159) aged fifteen months

The picture shows a pocket in the framework of calcified matrix substance such as the capillary creates when it reaches the under surface of the cartilage and is unable to advance. A fragment of calcified matrix substance can be seen at the top of the pocket. Presumably this represents a remnant which, if death had not supervened, would soon have been carried away. On the under surface of the cartilage which forms the roof of the pocket some cells, presumably mesenchymal cells which accompany the blood vessels, are present but do not show. The cells in the pocket are almost entirely connective tissue cells. It was such accumulations which made Schmorl regard connective tissue formations immediately under the cartilage as one of the very early signs of rickets. The cartilage above the pocket shows the yellow color and other degenerative changes described in the text.

framework. Later one finds that the vessel has made a definite advance into the cartilage substance and the yellow color has extended higher in the matrix framework.

Vessels may pass through the calcified framework and on into the cartilage just as under normal conditions. In some places in which the plane of the histological section makes it possible to trace what has happened one can see broad channels leading through the lattice framework to the under surface of the cartilage and vessels traveling up them and passing on into the cartilage. Obviously vessels break into the cartilage

wherever they can and the eruption need not be attended with abnormal signs

After the vessels have succeeded in reaching the interior of the proliferative cartilage they seem to grow rapidly. The picture of the invasion process, after penetration of the cartilage has taken place, is best obtained through the study of cleared preparations\*. When in the early stages of rickets these are examined, tiny sprouts appear to be growing from the end of the shaft. At a later stage the sprouts resemble small bushes, with respect to stem, branches and rounded outline. When the rickets is advanced, the picture is like this. From the end of the shaft a variable number of bush-like formations protrude. Some have a single stem from which fact it can be inferred that originally a single capillary broke through, others have a number of stems and a broad base, indicating that several capillaries must have broken through together. A great difference in size is noted. Some bushes may be so large that they extend well toward the top of the proliferative cartilage. Side by side with them may be smaller vessels. In yet other places the bud-like outgrowths are just commencing. The bushes are not distributed with any symmetry. The outer side of the upper end of the femur, for example, may show none but the inner side many. They may lie close together in one region and be widely separated in another. In general, even if close, they are separated by transparent cartilage but, if large, which means that the rachitic process must have lasted for a long time, they may meet. Most of them seem to be lying in a vertical direction but some may incline. If one inclines, examination shows that the surrounding cartilage has been displaced out of the vertical direction, presumably from the action of mechanical factors. The inclination of the bush depends on the inclination of the cartilage in which it is growing. The study of cleared preparations brings out the fact in the most striking way that blood vessels break into the cartilage at different times. The variations in size can mean only that penetration was easier at some points than at others.

If the rickets is mild and growth slow, one finds in the transparent preparations only the vessels from the end of the shaft, as just described. But if the rickets is of long duration and severe and the proliferative cartilage has accumulated in large mass, additional vessels, often very large ones, are seen descending from above and also entering from the sides.

\* The cleared specimens which we have employed are slabs of bone cut longitudinally through the cartilage shaft junction. They were made transparent with potassium hydroxide stained with alizarin and stored in glycerin.



Fig 6 a

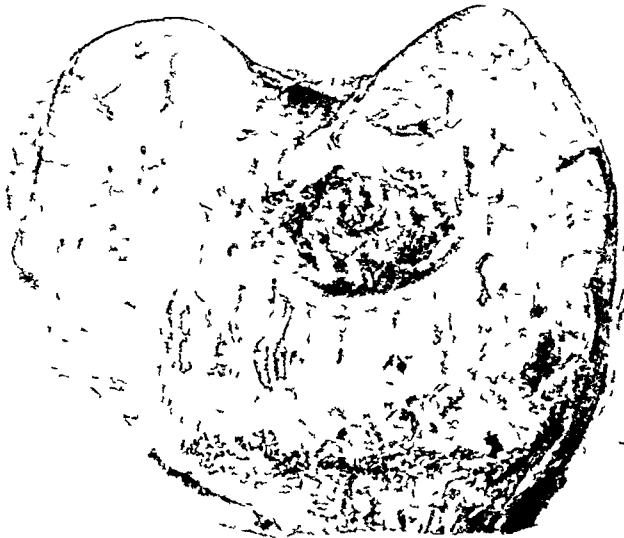


Fig 6 b

Fig 6—*a* Drawing from a cleared specimen of the upper end of tibia of a rabbit in which rickets had been experimentally produced. The vessels have been injected with india ink. The vascular bushes extending from the end of the shaft into the substance of the proliferative cartilage are beautifully shown. It will be observed that they have single stems. Obviously only single capillaries succeeded in breaking through. With the accumulation of proliferative cartilage which kept furnishing more soil they grew into large bushes. Between the bushes along the under surface of the cartilage are compression barriers which do not show in the drawing.

Fig 6—*b* Drawing from a cleared specimen of the lower end of the femur of L. H. (No 543) aged ten months. The picture shows the vessels protruding from the end of the shaft into the rachitic intermediate zone from below and the descending branches of the cartilage canals extending into it from above. The vessels which have penetrated from the end of the shaft have developed bush-like formations. They vary greatly in size. The variation is explained on the ground of different times of perforation through the barrier of compressed tissues at the cartilage shaft junction. It will be noted that branching has occurred immediately after penetration. The descending branches of the cartilage canals on the other hand have begun to branch only after reaching the zone of fully developed cartilage cells which is the one favorable for growth. Their stems therefore appear quite long. On the left hand side one can see the perichondrial vessels arching upwards into the proliferative cartilage and some smaller perichondrial ingrowths are visible on the right side. The effect in the original cleared specimen as seen under the dissecting microscope resembled pictures of submarine vegetation.

(Fig 6, *a*, *b*, *c* and *d*) The mass of cartilage is being invaded from all quarters

The vessels entering from above have the same general bush-like appearance as those extending upwards from below, but they have much longer stems, that is, they descend into the cartilage for some distance before they begin to branch, whereas the vessels rising out of the shaft branch immediately They vary in size, just as do the vessels ascending from the shaft, but, unlike the latter, show branching at widely different levels They are not disposed symmetrically and do not lie in any definite spatial relationship to the shaft vessels A descending vessel may be opposite an ascending, or a descending may extend downwards between ascending ones They remain separated from each other by the clear cartilage and in general do not join the upgrowing vessels from the shaft Particularly in the ribs, when the seat of severe rickets, the descending branches may reach enormous size, extending almost to the shaft When such is the case, vessels from the shaft are poorly developed

The vessels entering from the sides seem of minor importance They usually are small and turn upwards either immediately on entering the cartilage or after penetrating only a short distance They thus keep fairly close to the perichondrium Occasionally one is seen growing into the cartilage at right angles to its columns

We have obtained the distinct impression that the invading vessels tend to avoid each other, as if a negative chemotaxis existed, although in advanced rickets some of them may join When rickets begins to heal, they grow together with rapidity

The presence of vessels growing into the cartilage from the shaft is to be expected But in the normal bone, vessels do not invade the proliferative cartilage from elsewhere In order to make the origin of the invasion from these new quarters clear, it is necessary to explain briefly the vascular supply of the cartilage in the young child

*What are the cartilage canals?* The proliferative cartilage in the normal infant and young child has a blood supply of its own The vessels composing it, together with their connective tissue adnexa, are known as cartilage canals because of the broad channels which they create in the cartilage substance They contain an artery and (often two) veins and are surrounded by a thick investment of connective tissue in which run many small branches and capillaries The canal vessels are branches of the perichondrial vessels In the rib cartilage canals occur in the rest-



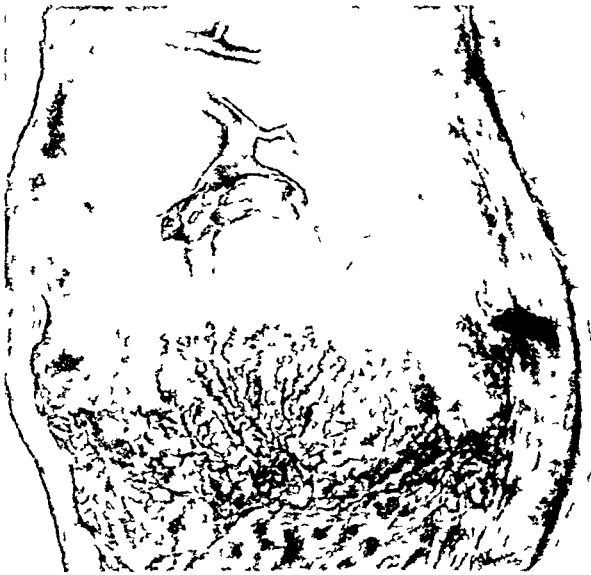


Fig 6c



Fig 6d

Fig 6—c Drawing of cleared specimen of the rib of D J (No 184) aged nine months. It shows quite beautifully the invasion of the cartilage by blood vessels springing from the end of the shaft. The vessels are long and thin. They are separated from each other by transparent cartilage. At the lower half of the central group of vessels chondro-osteoid trabeculae which have been developed about the stems have taken up lime salts. Their true trabecular nature can easily be detected because of their characteristic pattern. They appear black in the drawing. At the left, in the cartilage, close to the perichondrium, is a deposit of lime salts. It lies between vessels which have ascended from the shaft and the perichondrial membrane. Its pattern is rather poorly represented in the drawing because its texture is so fine as to defy delineation. On the right side a perichondrial vessel has arched out into the substance of the proliferative cartilage and some of its lowermost branches are growing at right angles into the latter. Just above the vessels is another deposit of lime salts in the cartilage. Its characteristic relationship to the blood vessels does not show particularly well in the drawing.

Fig 6—d Drawing of a cleared specimen of the rib of L H (No 345) aged ten months. The drawing shows beautifully an enormous accumulation of cartilage in the rachitic intermediate zone and correspondingly enormous descending branches of the cartilage canals which reach to the shaft. The drawing also shows perichondrial ingrowths on both sides. The enormous size of the descending branches of the cartilage canals and the very large size of the perichondrial vessels is due to the fact that essentially no invasion has taken place from the shaft itself. As pointed out in the text, blood vessels of perichondrial and cartilage canal origin attain great size, only when invasion from the shaft is almost entirely prevented by barrier formation. The drawing also illustrates how the ingrowing vessels no matter from which side they come seem to avoid each other. As soon as healing takes place they grow together.

ing as well as in the proliferative cartilage. Those supplying the proliferative cartilage are the ones which concern us. They penetrate the resting cartilage just above the level of the proliferative cartilage, skirt along the top of the latter giving off branches which end there and others which descend vertically toward the shaft. The descending branches, except in rare instances, appear to atrophy after a short distance. The thick surrounding cartilaginous walls, however, diminished and contracted into a band, are prolonged into the shaft. Often the osteoblasts build on it a massive trabecula which in the x-ray film can be seen extending far down into the shaft. It is very difficult to determine how far down blood vessels reach in these descending offshoots. Our general impression is that they extend only a short distance.

The vascular supply of the proliferative cartilage of the long bones having epiphyses is exactly similar to that in the ribs except that in them the proliferative cartilage does not have its private supply system. The vessels extending into it are branches of vessels which cluster around the nucleus of ossification. All the vessels of the cartilage canals terminate in curious bulbous formations. They do not anastomose and are, therefore, end vessels.

The cartilage canals are temporary structures, evidently necessary for nutrition of the cartilage in fast growing centers, for they atrophy and disappear later on in childhood. They are present in the puppy and young rabbit but not in the much smaller bones of the young rat in which diffusion distances are small.

*The mechanism of invasion.* In the proliferative cartilage of the fast growing epiphyses either single columns of cartilage cells or small groups of columns, forming fascicles, are the units. They are separated from each other by, relatively speaking, *thick* layers of matrix substance which constitute the major or essential framework of the proliferative cartilage. It is in this framework that the lime salts deposit. This framework persists after the cartilage cells have been cleared away by the invading blood vessels and on its surface the osteoblasts settle and build bone. The individual cells of the columns are separated from each other by their capsules and a thin intervening layer of matrix substance. These, fused together, form the intercellular cross partitions. The individual columns of the fascicles have also thin separating layers. These form the thin longitudinal partitions. Unless growth is very slow, lime salt deposition does not occur in them or in the cross partitions and both are destroyed by



Fig 7—Photomicrograph (high power view) from a microscopic section of the upper end of the femur of J W (No 957) aged three and a half months

The picture shows the *en masse* invasion which occurs characteristically in rickets. It is apparent that not only are the cartilage cells being attacked and destroyed but also the matrix framework. On the right side matrix framework denuded of its cells persists but in the center a partition between the vascular outgrowths contains cartilage cells. When osteoblasts settle on these partitions of matrix framework substance with or without cells and form osteoid coverings, the typical chondro-osteoid trabeculae, so characteristic of rickets, are produced.

the invading blood vessels. The course in normal endochondral bone formation, then, is as follows. When a single column of cartilage cells stands in the path of a capillary, the capillary breaking into the lacuna of the nearest cell encounters the cross partition above. After a delay required to overcome its resistance the capillary breaks through into the next lacuna, and so on. If a fascicle of columns lies in front, the capillary, spreading out, attacks the bottom-most layer of cells simultaneously. This process necessitates the destruction of the uncalcified longitudinal partitions between the columns in addition to the cross partitions.

In rickets the method of invasion of the cartilage is similar to that which occurs normally, when a fascicle of cartilage columns is dealt

with, that is, the blood vessel attacks simultaneously a group of cartilage columns and the matrix substance between. However, there is this important difference, that in rickets the capillary (or capillary group) attacks at the same time several different units, i.e., several columns and fascicles together and so encounters the thick matrix walls which separate the units from each other. When invasion of the proliferative cartilage is just commencing it is common in the histological preparation to see a capillary growing against three to four columns of cartilage cells and leaving a correspondingly wide track behind (Fig. 7). In severe protracted rickets one often finds an arc or horseshoe of dilated capillaries, representing the outermost branches of a large vascular bush, attacking simultaneously dozens of columns. With the increase in size of the invading blood vessels this *en masse* mode of destruction of the cartilage proceeds on larger and larger scale. When the invasion has gone on for a long time, one sometimes finds along the invasion surface large holes or cavities, evidently representing the lumina of blood vessels, which may or may not be filled with blood cells. Evidently the surface capillaries of the bush have become large channels (Fig. 8). The mechanism of destruction of cartilage in this *en masse* type of invasion, as seen under the microscope, appears to be as follows. The capsules of the cartilage cells obviously resist the vessels for a time and then one suddenly gives way. The vessel entering the lacuna creates for the moment a small salient at that point, then an adjacent cell capsule gives way, and thus the process continues. The destruction of the uncalcified matrix substance appears to be a steady process of solution or erosion.

In some instances the blood vessel completely destroys the matrix substance with the cells. This happens when the invading vessels are very large. Usually, however, more massive parts of the matrix framework, even though uncalcified, survive. On any framework which survives, osteoblasts settle and use it as a base for trabecular formation. This type of invasion process varies much with the degree of rickets. If the rickets is just beginning or is not severe, the invading vessels remain small. In that case, the massive parts of the framework of matrix substance quite regularly escape. It is when the disease is advanced and the invading units have become large channels that the massive parts of the framework go down with the cell capsules. The methods of invasion are exactly the same whether the vessel happens to take origin from the shaft, periosteum or cartilage.

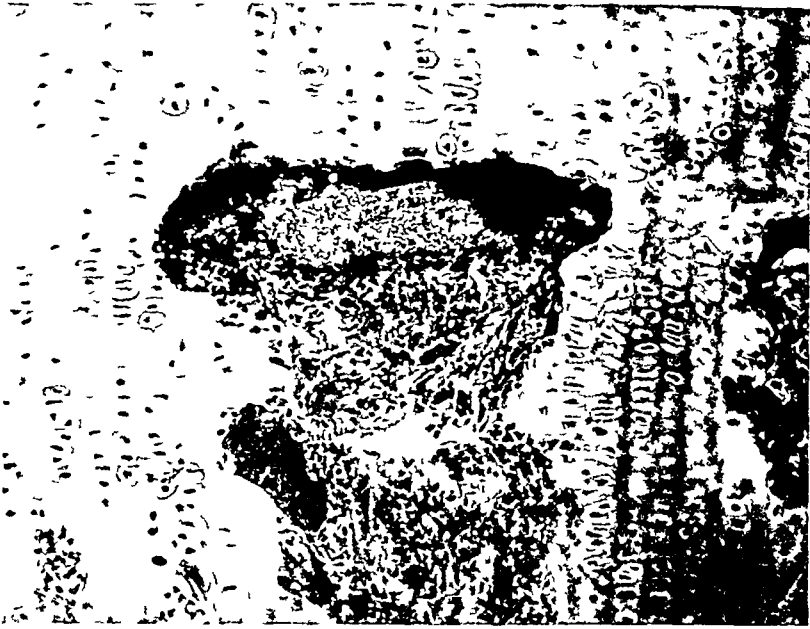


Fig 8—Photomicrograph (high power view) from a microscopic section of the tibia of a pupa in which rickets had been produced experimentally

The picture is shown to illustrate the enormous dilatation of the vessels which occupy the advancing surface of the vascular bush when the latter has attained large size. The vessels were injected with india ink. The black represents the greatly dilated lumina of the vascular channels. Surrounded in front and on the two sides by the india ink is a mass of blood cells. In the path of this invading mass of blood vessels both cartilage cells and matrix substance alike are being destroyed. On the right of the central vascular bush can be seen a partition of cartilage beyond which at the extreme right is another vascular bush, only partly shown.

It does not require any great degree of imagination to picture the gross effects on the proliferative cartilage of the irregular invasion. The invading blood vessels with their accompanying cells create ever enlarging holes, which, of course, are not actual cavities since they are filled with marrow elements brought by the blood vessels and contain in addition cartilage remnants. If one imagines a bush of invading blood vessels as a cast, and the hole in the enveloping cartilage as the mold, it will become apparent that the hole is not a simple cavity but has innumerable thin, sinuous recesses, larger ones corresponding to the larger branches, into which open smaller ones corresponding to the smaller branches, into

which in turn open still smaller ones corresponding to the smallest branches. What we are attempting to do by this comparison is to make clear that the invading blood vessels through their branching penetration reduce the enveloping cartilage to innumerable partitions. The osteoblasts, which accompany the blood vessels, settle on the surfaces just as they settle under normal conditions on the surfaces of the partitions of matrix framework and cover them over with osteoid bone. These partitions are frequently composed of both matrix substance and cells. Thus in rickets trabeculae are formed in the interior of which are cartilage cells. They belong to the chondro-osteoid trabeculae already mentioned. The chondro-osteoid trabeculae form an interlacing network and twist about in every direction without any semblance of plan. The reasons are evident enough in their mode of formation and the action of mechanical forces.

*Cause of the irregularity in the invasion.* Why is invasion of the proliferative cartilage so irregular in rickets? The explanation that has been given general acceptance is that of Schmorl.<sup>3</sup> He held that the blood vessels found it easier to grow through those places where calcification in the proliferative zone of the cartilage was defective than where it was normal. Accordingly, the capillaries chose the defective spots, and after their penetration, grew into large vessels and drew away the circulation from the calcified portions. Schmorl,<sup>3</sup> therefore, assumed defects in calcification of the cartilage as the essential primary condition. He offered no explanation why they occurred. Given the defects, the train of events developed in a natural sequence.

Schmorl<sup>3</sup> based his hypothesis on the study of histological preparations which he considered to represent early rickets. The illustrative picture which accompanied his article (see Table 1 in Schmorl's article) depicts beautifully blood vessels growing through large gaps in the zone of calcification. However, it shows that the rickets is already well advanced. We are under the impression that Schmorl's hypothesis is not correct. We give our reasons later.

In the rat the circulation at the cartilage-shaft border is not withdrawn at the onset of rickets. On the contrary, the capillaries all along seem to be distended with blood. The cause of the irregularity does not seem to lie, therefore, in any local circulatory failure. In the human being, also, at the beginning of rickets the circulation at the cartilage-shaft junction does not seem irregular.

In approaching the problem it is safe to proceed on the assumption that blood vessels will break through where they can. In some instances they are obstructed. First, obstructions may be subchondral. Complexes of branching or interconnecting trabeculae may be found under the cartilage which in the plane of the histological section appear to be preventing access of the blood vessels. These are encountered particularly at the slow growing cartilage-shaft junctions. When crushing of the calcified cartilaginous framework at the extreme end of the shaft has taken place, the bent spicules or fragments may block the regular channels of advance.

Second, the obstruction may lie in the cartilage at the cartilage-shaft junction. With the development of the rachitic state the cartilage as a whole becomes resistant, as will be explained later. A general resistance does not explain local differences, but it serves to delay initial penetration and may add to the effects of other factors, for example, compression, and cause irregularities in the circulation, as is pointed out below.

Local obstruction usually takes the form of compressed cartilage which is most apt to be situated at the points of impingement of individual trabeculae or groups of trabeculae. The cartilage may be compressed to such extent that it becomes stratified. Compressed cartilage evidently may furnish considerable obstruction to vascular penetration and even slight compression, some obstruction. If the compression has produced stratification, obstruction will be very great. In several of our specimens the stratified under surface of the cartilage seemed to have formed a resistant wall. We are under the impression that even slight disarrangements of the cartilage by which the cells are thrown out of line increased the difficulty of invasion.

On reaching the under surface of the cartilage the blood vessels will penetrate at once, if no obstruction exists. If, however, they are unable to go forward, they often spread laterally as when growth of normal cartilage is suddenly arrested for any reason and in so doing destroy the spicules of calcified matrix substance on either side, thereby creating pockets. From these they attempt to break through the barrier into the cartilage. This they will do ultimately.

Third, obstruction, theoretically, may exist in the form of a very heavy deposit of lime salts in the cartilage bordering on the shaft. Obviously, if lime salt deposition has been completely suspended, there can be no obstruction from that source. If the deposition ahead of the vessel is light, the vessel will carry it away very easily. Thus the invading vessels

do continually. We have found instances in which the bare capillaries themselves appeared to be successfully eroding calcified cartilaginous matrix framework. If the deposition in front of the vessel is heavy, it may act as an obstruction. We have evidence, however, that the larger vessels lying just under the cartilage so alter the cartilage immediately in front of them as to prevent it from taking up calcium salts. As a consequence inhibiting barriers of lime salt deposition do not ordinarily form in front of the vessels. This subject will be discussed later.

After the vessels have passed the barrier at the cartilage-shaft junction, they are free to expand. We hesitate to say with Schmorl<sup>1</sup> that those which have succeeded in penetrating take away the circulation from their fellows. With their increase in size, however, they do transmit increased blood volume, whereas the vessels which fail to penetrate remain small.

At the cartilage-shaft junctions of the slower growing epiphyses the causes of the irregularity of invasion are not entirely clear. Obstruction from compression may occur, but is not usual. At those locations vascular trunks appear to reach the under surface of the cartilage only at certain places. Between these places one finds heavy trabecular formations. In other words, channels exist between the trabecular formations leading to the under surface of the cartilage and the invasion of the cartilage takes place at the points where these channels open, i.e., where the blood vessels happen to lie.

Calcified matrix framework forms the boundaries of the apertures where the vessels have penetrated. Either the vessels that penetrate or others attack this calcified material from the sides. The erosion process goes on for as long as the rickets lasts. As the result, the original small holes of penetration become larger and larger. The masses of calcified matrix substance which intervene between the points of penetration become correspondingly reduced. After the rickets has persisted for a time the large holes and the small fragments of calcified matrix between give a most misleading idea in regard to the condition at the time when the rickets began.

*Why do the apparently withered branches of the cartilage canals come to life and the perichondrial vessels grow out into the cartilage?* When the vessels of the shaft succeed in budding into the cartilage it is easy to understand why they should continue to grow. But why should the vessels of the cartilage canals and the perichondrial vessels



join in the invasion? The mere fact that capillaries from the end of the shaft normally grow into the proliferative cartilage makes it seem certain that the cells of the latter when fully developed must possess chemotactic properties. In cases of rickets we can often follow small arteries through the shaft and observe that on arriving in contact with the cartilage they undergo extreme dilatation. When the fully grown cartilage cells accumulate about the descending branches of the cartilage canals, they must stimulate the capillaries in the canals to growth exactly as they do the capillaries of the shaft. How it is accomplished is unknown. The situation must be similar to that when blood clot forms or dead tissue develops in the neighborhood of capillaries. As a possible reason why the budding out process does not occur under normal conditions we point to the thinness of the layer of fully developed cartilage cells and the fact that it is taken up as fast as formed by the shaft vessels.

The budding of the canals does not occur unless the disease is severe and prolonged and may not occur even then. One branch may bud and another not, or the level at which budding occurs may be different. These variations may be explicable on the basis of differences in length of the blood vessels in the descending branches.

The participation of the perichondrial vessels must be, also, in response to chemotactic influences originating in the accumulated mass of fully mature cartilage cells.

Schmidt<sup>28</sup> and Schmorl<sup>29</sup> seem to regard the invasion from the cartilage canals in rickets as not only abnormal but most injurious. We admit that it never occurs normally. It is obviously, however, an effort to compensate for the inability of the shaft vessels alone to meet the situation and as such it is most successful. When the healing process once begins, it is completed much more rapidly as the result of the previous coparticipation of the vascular system of cartilage and perichondrium in the invasion process.

Both Schmidt<sup>28</sup> and Schmorl<sup>29</sup> hold that the cartilage canals are chief agents for conversion of cartilage in rickets. Our study of club bones demonstrates that such is not the case. In the great majority of instances the vessels from the shaft take the entire or else the major part of the burden. However, in the ribs and occasionally in other fast growing bones the canals dominate the picture, becoming enormous and reaching to the cartilage-shaft border. In that case the invading vessels from the shaft remain very small. Whether or not the cartilage

develop to large size depends, first, on the amount of accumulation of the mature proliferative cartilage and, second, the extent and effectiveness of the obstruction at the cartilage-shaft junction. When the canals become enormous, the shaft vessels have been effectually blocked for a long time.

*The changes in the cartilage.* We are much handicapped in studying the cartilage in the infant because of difficulties in interpretation. Standards of comparison are lacking, owing to variations in age and growth rates at the various bone ends. Also, we are not sure that the disease from which the infant died, in particular if accompanied by extreme dehydration, may not have altered the cartilage. Recently, since we have become aware of the frequency of vitamin C deficiency, we have often felt insecure lest it might have been a factor in altering the cartilage cells. Finally, in certain instances it has been difficult to exclude congenital syphilis which may affect the cartilage. Hence, we are particularly grateful to Dodds and Cameron<sup>6</sup> for their beautiful studies of the effects of rickets on the proliferative cartilage in the rat.

We have already mentioned that Dodds and Cameron<sup>6</sup> found the fully grown cell of the proliferative cartilage shorter than normal, though of the same breadth. We have thought that in some cases of human rickets the fully grown cell was smaller and more ball-like and possibly that the capsule was slightly thicker.

We now call attention to certain degenerative changes which are particularly characteristic, if the disease is at all severe.

*Pseudo-osteoid transformation.* We have chosen this designation because it denotes what actually transpires, namely, that the cartilage becomes changed into a form which greatly resembles the osteoid tissue produced by the osteoblasts. If we try to trace the process, it is somewhat as follows. The matrix substance becomes yellow and the large blue-staining cartilage cells and their capsules begin to lose their color. The cell capsule retains its blue stain better than the cell body and the nucleus even better than the capsule. Both cell and cell capsule shrink. The matrix substance increases in amount and the cell capsule becomes thin. Finally the cartilage cell with its lacuna becomes reduced to the size of a bone corpuscle and in its setting in the matrix substance looks like one. There are great variations. In some cases the cartilage cells remain large. The nucleus and capsule retain the blue stain but the cell body becomes clear. Later the capsule and still later the nucleus lose

their blue stain. The capsule seems to merge with the matrix but retains at the cell margin its refractile properties. Finally, the cell without any color looks like a ghost of itself and can be identified chiefly because of differences in refraction of its capsule. All this takes place with little shrinkage. In some instances the cells and capsules contract to very small size, retaining the while their purple color and looking like minute balls. In general, the closer to the blood vessels, the more the condition resembles osteoid and the further away the more numerous are the cells which still retain normal features (staining properties, size, etc.). There is evidently great difference, also, in rate of change. In some instances it must be abrupt, in others gradual.

*Development of bizarre forms.* The cartilage capsules and cells shrink and assume a globular or spheroidal form, at the same time staining so heavily with hematoxylin that the shade is a deep purple. Depending on the degree of contraction, these cells show great variations in size, from dimensions of the full sized proliferative cartilage cell to those of the bone corpuscle. Occasional cells contain dumbbell-shaped nuclei and others double nuclei, as if division had taken place. These peculiar cells are apt to be found in clusters at the tips of the peninsulae or in fringes along the sides, intermingled with other abnormal forms. Occasionally one sees them in the heart of chondro-osteoid trabeculae well down in the shaft. Ultimately, these cells lose the power of taking hematoxylin stain, become smaller and take on the appearance of bone corpuscles.

We think that these degenerative transformations of the cartilage are connected with incomplete exposure to the blood. If the exposure is fairly rapid, the transformation to the bone corpuscle-like forms is rapid. If very slow, the various intermediate forms develop. Under normal conditions the capillary is in contact for only a brief time with the capsule before penetration takes place. According to Dodds and Cameron's<sup>6</sup> calculations, a capillary must penetrate seven cartilage-cell capsules daily in order to meet the requirements of normal growth in the young rat. Under the irregular invasion of rickets the cartilage in various localities must remain for some time in sufficient proximity to the blood to be affected by its pH or some other factor without being actually attacked. Under those circumstances it passes over into pseudo-osteoid, with or without the production of the curious intermediate forms. We believe that the cartilage cell cannot be exposed to the influences of the blood

and remain cartilage. A change is forced. Harris,<sup>30</sup> Ham,<sup>31</sup> Wolbach<sup>22</sup> and others all are convinced that normally the cartilage cell is dead at the time when penetration occurs. Dodds and Cameron<sup>6</sup> have reported finding cartilage cells in normal bone which seemed to be excellently preserved after liberation from the capsule and we have made the same observation. We used to think that in rickets actual metaplasia took place, i e., that the cartilage cells, having been reduced to the size and appearance of bone corpuscles, became such. Further studies, however, convinced us that they actually died. An inspection of old chondro-osteoid trabeculae will often reveal slit-like spaces empty of cells, which represent the original lacunae and can be identified only because of retention of the refractile qualities of the walls.

The chemical changes in the blood peculiar to rickets may be a determining factor. One sees degenerative changes in the cartilage in scurvy and congenital syphilis, but not just like the ones described.

It is necessary to mention other degenerative changes. In many cases of severe rickets the fully grown cells seem to be generally changed. They are very small and irregular and the matrix substance greatly increased. The columnar arrangement is poorly preserved, so that the cells as a whole have a jumbled appearance. The staining reactions to hematoxylin and eosin are preserved. In some of these cases one finds that the cartilage at the junction with the shaft is greatly compressed and we have wondered if the condition of the cells described might not be due to failure in nutritive supply. It is also possible that pressure influences may be responsible for the changes.

In the puppy suffering from rickets we have encountered actual death of the cartilage cells. The cells affected were in family groups, that is, columns of cartilage cells would be necrotic whereas neighboring columns would seem fairly normal. In the two animals studied the accumulation of the proliferative cartilage was nothing short of enormous, and the cartilage-shaft border was so compressed that one gained the impression it might have been difficultly pervious or actually impervious to the lymph.

Cartilage may become completely necrotic. It is common in the rat to find these necrotic areas at the cartilage-shaft junction. They are often hemispherical and are sharply circumscribed. One occasionally finds them in the human being in the same situations. Dodds and Cameron<sup>6</sup> ascribe the necrosis to the action of mechanical factors. We have found

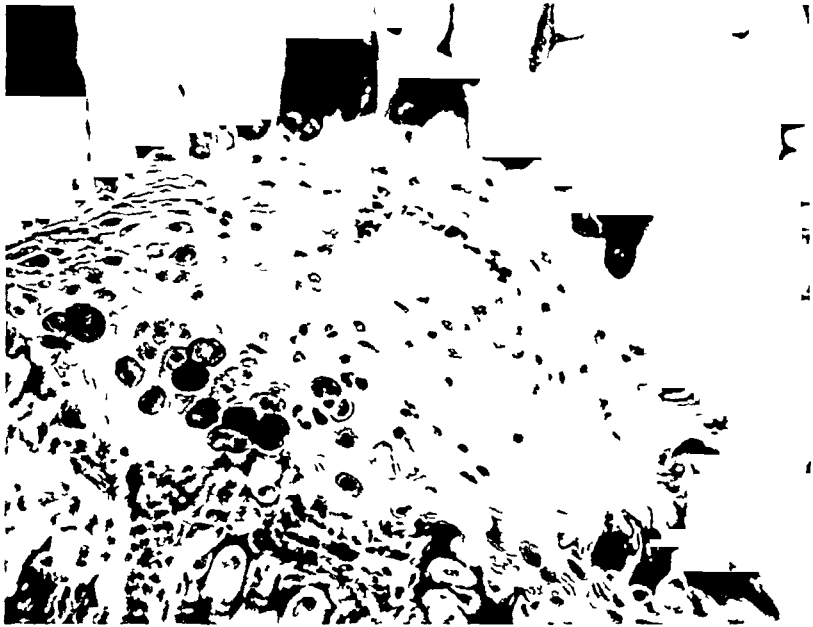


Fig 9—Photomicrograph (high power view) from a microscopic section of the upper end of the tibia of a rat in which the rickets had reached an advanced stage of development

The picture shows one of the areas of dead and dying cartilage cells lying just above the shaft. In the lower central and left hand regions one can see the phenomenon of rejuvenation of cartilage cells, described by Dodds and Cameron. No blood vessels are growing into the area from the shaft. However, a blood vessel, partly injected with india ink, can be seen arching across the dead area in its upper part. We are inclined to think that the occasional vessels seen in these dead areas have found entrance after the death of the tissue has occurred.

areas in which no evidence existed in the tissues themselves either of compression or tension, but we could not exclude the possibility of the intermittent action of mechanical factors and have wondered if cell death resulted from failure in nutritive supply. The necrotic areas were bounded on the shaft side by barriers through which capillaries were not penetrating. Schmorl and Lossen<sup>26</sup> produced such necrosis in the normal rabbit by cutting away bone immediately under the cartilage. Where granulation tissue had grown into the cavity, the overlying cartilage cells remained alive but where the cavity was filled with blood clot and debris the cartilage cells had undergone complete necrosis. In the case of the rat, one sees in some instances blood vessels traversing the necrotic

areas We have been inclined to think, however, that they had found entrance after the necrosis had occurred Between some of these areas of necrosis and the shaft we have found scattered cartilage cells, not only alive but apparently dividing, the rejuvenation described by Dodds and Cameron<sup>6</sup> (Fig 9) We have thought that perhaps just sufficient lymph passed the barrier to keep alive these cells and caused them to undergo these curious changes

*Is the proliferative cartilage abnormally resistant?* The obstruction to invasion seems to lie chiefly at the cartilage-shaft junction and to be of a mechanical nature, as already pointed out At the extreme periphery where compression does not occur so readily and the lines of normal growth are better preserved, invasion is often deep But conditions may be different there than in the interior on account of the proximity of the perichondrial circulation In the human being, dog, rabbit and rat invasion may be entirely absent or poorly developed in one place but in an adjacent place approximate the normal The fact that invasion can extend to the normal limit anywhere might be used as an argument against special resistance in the cartilage itself However, if one remembers that growth of the proliferative cartilage is diminished or actually stopped, as Dodds and Cameron<sup>6</sup> showed was the case in the rat, slowly advancing vessels, if given time, would penetrate to their limit Chemical studies have not been made on the cartilage in rickets, so far as we know, though the pH has been shown to be unchanged (Pierce<sup>32</sup>) Although Dodds and Cameron<sup>6</sup> have demonstrated that the cartilage cell is reduced in size (in the rat) and we have pointed out that the cartilage does undergo most peculiar changes, these peculiarities do not necessarily signify that the cartilage is changed chemically The fault may lie not in the cartilage cell but in the altered chemical conditions in the blood or perhaps in the lack of the directing influence of the normal calcium deposits Proof, however, that the proliferative cartilage is actually more resistant is afforded by treatment, for when vitamin D has produced its effect, the cartilage is rapidly penetrated and removed

*The rachitic intermediate zone (or metaphysis)* The steady accumulation of proliferative cartilage and the irregular invasion and clumsy conversion of the cartilage by the blood vessels are responsible for the formation between the end of the shaft and the generating zones of the proliferative cartilage of a hodge-podge, known as the rachitic intermediate zone or, in the German literature, rachitic metaphysis If one

will but think of it as a large mass of proliferative cartilage containing in its interior the vascular bushes which have grown into it from below and perhaps, also have entered from above and the sides, and remember how the vascular bushes bring marrow cells with them and break up the cartilage into chondro-osteoid trabeculae, the histological picture ought to be clear. The masses of proliferative cartilage which extend toward the shaft as peninsulae or ribbons or appear as islands, represent merely the remnants of the parts originally skipped in the invasion process. The blood vessels are the trunks, stems, and terminal branches of the vascular bushes, whether entering from the side of the shaft, the cartilage or perichondrium. Their bush-like formation is not apparent any more than the structure of a tree would be evident in any section in a single plane, unless it chanced to be vertical through the trunk. The chondro-osteoid trabeculae represent the partitions of the matrix framework of the cartilage, freed of cartilage cells by the blood vessels and covered by the osteoblasts with osteoid bone. Those which contain inclusions of cartilage cells represent the thicker partitions of cartilage between vascular branches on which osteoblasts have settled as if they consisted of matrix substance alone. The cells, lining the chondro-osteoid trabeculae, are osteoblasts with an occasional osteoclast. The spaces between the chondro-osteoid trabeculae are very narrow, as Dodds and Cameron<sup>6</sup> point out, and are filled by the blood vessels and a sparse connective tissue network. Marrow cells are represented only by stragglers. As might be expected, the chondro-osteoid trabeculae are most numerous in those parts which were invaded first, i e., on the shaft side. The cells of the peninsulae are normal looking fully developed cartilage cells, but in the peripheral regions and especially at the tips are found the pseudo-osteoid transformations and the bizarre forms of cells which have been described. Here and there deposits of calcium salts may be found, marking focal areas where some time in the past local conditions happened to be so much more favorable than elsewhere for lime salt deposition as to confer on the areas in question a selectivity. It will be noted that many of these lie at the tips of the peninsulae of cartilage but they may occur in various places and, if healing has commenced in earnest, they often run crosswise in strata formations. Always in the rachitic metaphysis one can see the effects of the operation of mechanical forces.

*Evidences of the operation of mechanical forces* In many places in the rachitic intermediate zone one can see the marks of mechanical

forces We have already described the compression changes at the cartilage-shaft junction The peninsulae of proliferative cartilage which extend from the main mass toward the shaft are almost always bent at some part of their course and occasionally are even doubled back It is common to find groups of cells which have evidently been compressed or stretched The cartilage columns at the periphery of the proliferative zone may fan at angles of 45 or even 90 degrees The entire phenomenon of cupping is a response to mechanical influences Cell columns at the cartilage-shaft border may be stretched apart In the case of the costochondral junction, especially, tension becomes a most important factor and may cause the lower part of the intermediate zone to give way, so that the upper part is pulled around against the outer surface of the shaft

Mechanical forces seem to be operating aimlessly On the contrary, they determine the subsequent architectural arrangement Before explaining how this comes to pass, we must record our observations on calcification of the cartilage in rickets since they supply the clues to the subject

*Observations on the calcium deposits which occur sporadically and during the course of healing in the intermediate zone* Since calcification is selective, it follows that it must be determined by two conditions, one general, the other local The general condition is represented by some chemical equilibrium which we have symbolized by the SP, for calcium phosphate in the blood The local conditions determining calcification are unknown Robison<sup>33</sup> has proposed phosphatase which the cartilage cells are supposed to elaborate Shear\* has suggested, as another possibility, a slight shift in the pH to the alkaline side at the calcification site If the SP is high enough, calcification will occur in bone and cartilage, even if the local conditions are not especially favorable If the SP is sufficiently low, calcification will not occur anywhere, irrespective of the local site If the SP is at certain intermediate values, calcification will take place only if the local conditions are in some way peculiarly favorable It is possible to postulate, therefore, that the necessary local factors are present whenever lime salts deposit selectively, also, that the sites of deposition are within the diffusion range of the lymph, since the lymph is the only source of the necessary material

We have obtained information on the subject of calcification from



the examination of cleared specimens of rachitic bones in which the deposits of lime salts stained with alizarin show with clearness in the transparent medium of the cartilage

Before proceeding to the results of our studies, however, it is necessary to point out that lime salts deposit in two different kinds of tissue in the rachitic intermediate zone, namely, in the chondro-osteoid trabeculae and in the proliferative cartilage. In cleared specimens one can easily distinguish the trabecular deposits from those which have occurred in the cartilage. When deposition takes place in the chondro-osteoid trabeculae, the pattern seen is coarse and plainly that of trabeculae, whereas when the deposits occur in the proliferative cartilage, the pattern is fine and regular, evidently that of the matrix framework. It is interesting that in some cases calcification of the chondro-osteoid trabeculae precedes calcification of the cartilage. It is common, however, to find calcification occurring focally at the same time in both tissues. Our present observations are limited to the study of lime salt depositions in the cartilage.

Muller<sup>11</sup> first called attention to the fact that, when rickets healed, calcification took place in a stratum of the proliferative cartilage which was situated at some distance from the end of the shaft. The lime salts skipped the cartilage adjacent to the end of the shaft and chose cartilage at some distance beyond. Muller<sup>11</sup> further recognized that the stratum selected corresponded in its situation to the so-called provisional zone of calcification, i.e., the zone in which deposition would have occurred if rickets had never supervened. He also commented that the cartilage chosen must be chemically different from the rest. When we examine cleared specimens of rachitic bones, especially if treatment was commenced a few weeks before death, we often find the stratum of lime salt deposition described by Muller (Fig. 10, *a*). It is always separated from the end of the shaft by transparent cartilage, the thickness of which varies with the length of the intermediate zone. We find that it represents, relatively speaking, a smooth surface on the upper side but an irregular surface on the lower (shaft side). Obviously, on the upper side there is a smooth limiting surface of some kind. We observe, also, that the stratum of lime salts extends higher and is hence thicker at the extreme periphery than elsewhere and also that it does not reach the perichondrial membrane but is separated from the latter by a layer of transparent cartilage. The surface which it presents toward

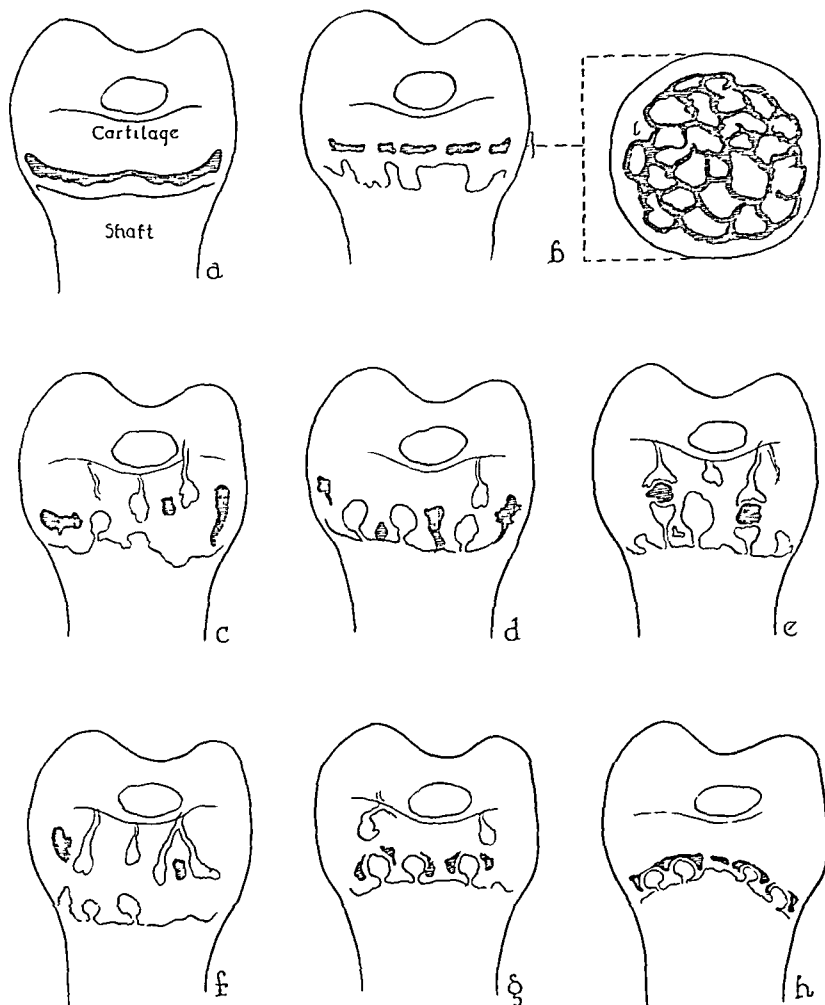


Fig 10—Diagrammatic drawings in single planes, showing relationships of lime salt depositions in cleared specimens

a Stratum of lime salt deposition in substance of proliferative cartilage. The distribution is zonal

b Deposits of lime salts in zonal arrangement. In reality the stratum of lime salt deposition is full of defective areas caused by the inhibitory influences of the blood vessels. The circular drawing to the right showing the stratum on end makes clear why the deposit seems fragmentary in single plane preparations

c A lime salt deposit paralleling perichondrial membrane

d Lime salt deposits between vascular bushes growing out of the end of the shaft

e Lime salt deposits between vascular bushes growing out of the end of the shaft and the descending branches from the cartilage canals

f A lime salt deposit between descending branches of cartilage canals and one between descending branch of cartilage canal and perichondrial membrane

g and h Dome formation over vascular bushes partial and complete

For a complete understanding of the drawings the reader must consult the text

the perichondrial membrane is smooth and parallel to the latter. Such strata of lime salt deposits in the substance of the cartilage are rarely complete, and are only so when the rickets is comparatively early and invasion has not developed to any extent. If the invasion from the shaft has reached the point at which the blood vessels come close to, or extend into or actually pass through the stratum, we find that the latter is defective and that the defective areas are circular and correspond to the location of the vessels. In other words, where the vessels ascend from the shaft, lime salt deposition has not taken place, but it has taken place between. When under such circumstances we examine the stratum of lime salt deposition from above, we find that it is filled with crater-like holes (Fig 10, *b*) and that in the hole or just below or protruding above are bushes of blood vessels. The same conditions hold true in case of the descending branches from the cartilage canals. Where the latter approach the stratum of lime salt deposits from above or actually pass through, circular apertures exist. When the stratum shows this perforate condition in the cleared specimens, the deposits appear in the histological sections as fragments which, however, are in line with each other in a zonal curve.

Calcium deposits may also form parallel to the perichondrial membrane (Fig 10, *c*). In that case they do not touch the perichondrial membrane but are separated from it by a clear layer of cartilage cells. The surface which presents toward the perichondrium is smooth. Obviously, there must be some smooth surface of limitation on the perichondrial side which prevents the spread of calcification in that direction. We have observed in the case of the puppy having rickets that the pattern of the deposits corresponded to the pattern of the vascular network of the perichondrium, but we were unable to determine the exact relationships.

Depositions of lime salts in the cartilage also occur in definite relationship to the blood vessels growing into it from the end of the shaft, the perichondrium or the cartilage canals. The favorite situation is between blood vessels (Fig 10, *d*). Thus, it is common to find deposits between vascular bushes emerging from the end of the shaft or between a vascular bush and perichondrial vessels. If cartilage canals play an important part in the invasion, one may find them lying between a vascular bush growing out of the end of the shaft and a descending branch of a cartilage canal (Fig 10, *e*). Occasionally one finds

them between two descending branches of cartilage canals or between the latter and perichondrial vessels (Fig 10, *f*) When lime salt deposits occur in relationship to the blood vessels growing into the cartilage, they are separated from the latter by a zone of clear cartilage. Moreover, if the vascular bush presents an even rounded contour, the surface of the lime salt deposit facing the bush is correspondingly concave and smooth, paralleling the surface of the bush. Most commonly the deposits of lime salts lie opposite the middle level of the bushes. Quite often, however, they are continuous with the shaft. In that case, the appearance is that of promontories or pillars of calcified material rising out of the top of the shaft between the vascular bushes (Fig 10, *d*). If lime salt deposits exist between the vascular bushes and the perichondrial membranes, it is quite common for them at one point or another to join lime salt deposits in the perichondrial membrane by means of an arm or arms. In that event it can sometimes be demonstrated that vessels extend from the perichondrium into the substance of the cartilage above and below the extending arm, separated by clear cartilage. Occasionally we encounter lime salt deposits lying off an isolated vascular bush (Fig 10, *g*). Thus, two vascular bushes are not essential for the production of lime salt deposits in the cartilage. Moreover, we have found instances in which the lime salt deposits, thick at the sides of the bush, extended as if to surmount the entire bush. However, as the summit was approached, the lime salt deposition became thinner and over the top stopped altogether (Fig 10, *h*). In one instance, we have found lime salt deposits, which were thick between bushes, extending completely over the summits, forming domes. However, the tops of the domes were much thinner than the rest and in some instances were incomplete. In this instance and in other instances in which domes had started to form, the proliferative cartilage was relatively short (femur). The impression was obtained that the uppermost lime salt deposits were close to or actually in the top of the zone of large cartilage cells where zonal deposition of lime salts occurs, in other words, that the calcification might be a combination of perivascular and zonal deposits. We have not seen any indication of dome formation over the vascular bushes when the proliferative cartilage was exceedingly deep, as in the case of the ribs.

It is difficult to think of a single hypothesis which explains the location of these focal depositions of lime salts in the rachitic intermediate zone. One factor is certain, namely, the lymph, for the only source of

lime salts is the lymph, as already stated. When deposits lie between vascular bushes, the source of the lymph must be from the bushes themselves. When the lime salts deposit in stratum formation across the cartilage, the source of the lymph is presumably from the end of the shaft. At least, in a single experiment reported by Schmorl and Lossen<sup>26</sup> lime salt deposition occurred in stratum formation in the cartilage above the points where circulation in the shaft had been preserved but failed to occur above the points where it had been blocked by dead tissue. Another factor may be continuity. We have gained the impression that lime salt deposition occurring at a given focus may extend from that focus by continuity. One reason for thinking this is that lime salt deposition, when rickets heals, often tends to extend in processes which become more tenuous until they stop altogether. Formerly, we explained stratum formation on the hypothesis of ageing of the cartilage cells. We thought that, when the cartilage cell developed to a certain maturity, it generated the local factors necessary for lime salt deposition but, if deposition did not ensue, they were lost. It is impossible, however, to explain the sheets of lime salt deposit which parallel the perichondrial membrane or the deposits which form around the vascular bushes on the ground of ageing of the cartilage cell. The formation of these deposits must depend on circulatory conditions. The tendency for calcification to take place in the cartilage intervening between blood vessels suggests that a predisposing factor may be lymph stasis. We are inclined to think that the deposition around blood vessels is determined by the diffusion of the lymph. If the lymph flow is sufficiently brisk, so that some essential factors, such as oxygen tension, are maintained, lime salt deposition is inhibited, i.e., phosphatase is destroyed or the pH optimal for the selective deposition of lime salts, is prevented from developing. If, however, the lymph flow is sufficiently diminished, the conditions favorable for lime salt deposition become fulfilled. In order to explain the absence of the formation of lime salts above the vascular bushes growing out of the end of the shaft, or below the descending branches of the cartilage canals, according to this hypothesis, it is necessary to think that the diffusion of lymph takes place much more readily along the vertical lines of the cartilage, i.e., up and down in the direction of its columns of cells and of the matrix framework than across them. It is possible that the same necessary local conditions may be caused to develop in two totally different ways. It seems difficult to explain the zonal distribution of lime salts

on circulatory grounds alone. If, however, further studies should prove that anatomical conditions favored lymph stasis in the stratum of cartilage immediately underlying the generating zones, the single hypothesis of variations in the lymph flow would suffice. In any case, the observations that lime salt deposits tend to develop in the cartilage at the sides of and especially between blood vessels and tend to avoid the pathways of vertical growth is of great practical importance, because it offers an explanation for the variations in calcification at the cartilage-shaft junction in rickets. Under the conditions of rickets the cartilage in front of the dilated blood vessels is prevented from developing its selective power to take lime salts out of the blood. We believe, therefore, that the generally accepted hypothesis of Schmorl<sup>3</sup> to explain the irregular invasion which occurs in rickets is wrong. The mere fact that lime salt deposition fails in the pathways of the descending branches of the cartilage canals is by itself sufficient to destroy Schmorl's<sup>3</sup> hypothesis, because the descending branches come from widely separated fixed points and occupy fixed lines in the cartilage and have no ability to conform in their growth to pre-existing holes in the zone of calcification. Schmorl<sup>3</sup> put the cart before the horse.

Our observations of the relationship of the lime salt deposits to the vascular bushes, which represent large vascular complexes, are perfectly clear. No doubt whatsoever exists that the large vessels inhibit the deposition of lime salts from occurring along their paths of growth. When the invading units are of very small size, the cleared specimen technique is too coarse to reveal relationships. We believe, however, that the principle that the blood vessels under the conditions of rickets inhibit lime salt deposition in their pathways is the cause of the irregular deposition of lime salts at the cartilage-shaft junction from the very beginning. The minute defects in calcification are to be referred to minute variations in the circulation in the shaft immediately beneath. As the variations in the circulation at the end of the shaft become greater, the corresponding defects in calcification become greater, until the phenomenon becomes so well defined as to be obvious in the cleared preparation.

We should like to add in conclusion that the relationships between lime salt depositions in the cartilage and the circulation are not apparent in the single plane of histological preparations. Visualization in three dimensions is essential.

*How mechanical forces actually determine the architectural arrange-*

*ment of the intermediate zone* The epiphyseal cartilage, transmitting its superimposed weight, rests on the trabecular framework. Not all the trabeculae function equally as supporting piers. Some groups act as main supports, others minor or secondary supports. These latter, presumably, are destined soon to be removed. The compression of the cartilage is greatest, naturally over the parts of the trabecular framework which function as major supports. The vessels penetrate the cartilage where it is least compressed or not compressed at all. It follows that they enter between the major points of support. It is a noteworthy and most important fact that, as just explained, when lime salts fall, they avoid the cartilage in front of the vessels and choose the cartilage of the sides, *i e., in front of the main supporting piers*. Because the matrix framework of the cartilage in front of the supporting piers has been compressed, the lime salt deposits are of an extremely dense character. The parts of the proliferative cartilage which remain untouched by the invading vessels and hence persist as peninsulae are those which have been protected by the compression barriers. It, therefore, comes to pass that the supporting piers, the deposits of lime salts and the peninsulae of proliferative cartilage are in line with each other. The architectural arrangement, then, which develops as the disease extends, is this. The weight-bearing complexes comprising trabecular piers, calcified matrix formations, and peninsulae of proliferative cartilage alternate with the invasion complexes of superfluous parts of the trabecular framework, vascular bushes with their cellular components and the lime salt free areas. Since the weight-bearing lines in the bones pass through the peninsulae, it is small wonder that these masses of cartilage in particular show the effects of pressure (Fig 11)

*The architectural arrangement in chronic rickets* In chronic rickets lime salts keep depositing but only in certain places. The areas free from lime salt deposition lie at the invasion sites. The deposits are situated between them. They seem particularly dense. The extreme density is due to two factors, first compression and second, slow growth. Compression, by flattening the lacunae, collapses the framework, so that, when it becomes permeated with lime salts, the deposition is condensed. Slow growth, which is certainly very common in, if not a regular feature of, chronic rickets, results in an extension of the calcification into the cross and minor longitudinal partitions. Granted that in rickets a modicum of lime salt deposition continues, the alternation of lime salt free invasion



Fig 11—Photomicrograph (low power view) from a microscopic section of the upper end of the tibia of a rat

The picture shows beautifully the effect of pressure on a peninsula of proliferative cartilage extending from the main mass towards the shaft. In some instances compression may be so great that a peninsula is actually bent back on itself. The picture also shows beautifully the chondrosteoid trabeculae (*T*). These soft trabeculae have probably been compressed and bent to the same extent as the peninsula of proliferative cartilage. But there is no means of knowing what their original architectural arrangement was. At the tip end of the peninsula a fragmentary deposit of lime salts is present. The peninsulae of proliferative cartilage almost always show such deposits at their tips.

areas and intervening heavy deposits of lime salts in deformed and compressed cartilaginous matrix framework is exactly what would be anticipated from the principles laid down in the foregoing discussions (Fig 12)

*Does the defective deposition of lime salts explain all the pathological changes?* Schmorl<sup>3</sup> held that every pathological change in the cartilage and bone was due to lack of lime salt deposits, and Dodds and Cameron<sup>6</sup> have championed this view. The argument is as follows. The lime salts, while attacking the proliferative cartilage, keep the capillaries confined in metallic tubes and force them to limit their activities to the single columns or fascicular groups lying ahead of them. When lime salts cease



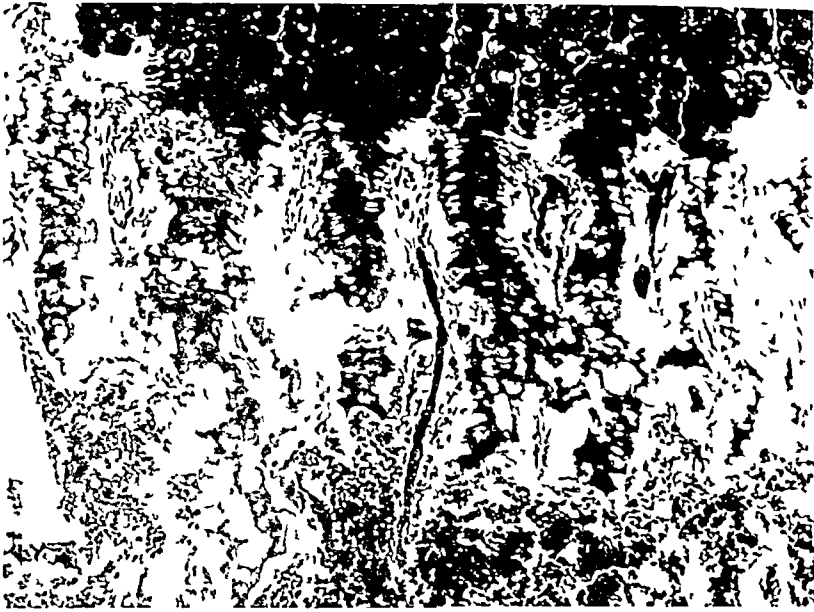


Fig 12—Photomicrograph (high power view) from a microscopic section of the upper end of the tibia of a rat

The rickets has assumed a chronic form. The circulation was injected at the time of death with india ink. It will be observed that invasion areas alternate with areas of dense lime salt deposit. The dense lime salt deposits lie in greatly deformed and crushed formations of matrix framework. The reasons for this will be found in the text.

to deposit, the capillaries destroy the matrix walls as well as the lacunae and, therefore, no longer remain confined. Their liberation allows freedom of growth, so that individual vessels reach great size, and causes the substitution of the *en masse* for the normal invasion. *En masse* invasion is inefficient, since it involves destruction of the uncalcified matrix framework together with the cells and the framework offers more resistance than the cell partitions alone.

Undoubtedly the failure in lime salt deposition explains the changes which transpire in the shaft, the irregularity of the invasion of the cartilage, the large size of the invading vessels and the *en masse* invasion. But does it explain the increased resistance of the cartilage? When one investigates, in order to learn if the uncalcified matrix framework is serving as an obstacle, one occasionally finds a capillary traversing it as if by preference. However, in the main, even in severe rickets, the

invasion paths seem to be preferentially along the cells. Matrix substance, when calcified, obviously constitutes an obstacle, for it is common to find a spicule projecting and holding back a capillary which has already caused the cartilage on either side to give way. In the *en masse* invasion we do not find such exposed ends of uncalcified matrix framework protruding along the invasion surface. On the contrary, the framework seems to be destroyed with the cells and in occasional places even in advance of them. The framework, when uncalcified, offers little greater resistance than the cell capsules. But there is a reason for thinking that it does offer a little greater resistance, since the more massive parts of it tend to survive the attack of the vessels. The increased resistance of the cartilage may, therefore, be explicable on the "mechanical" hypothesis.

There are some reasons, however, for attributing the increased resistance, in part at least, to altered chemical conditions which prevent the matrix substance when in contact with the capillary from undergoing normal solution. For example, if the "mechanical" theory were the entire explanation, we should expect that the vessels would pass more easily where calcification exists than where it is defective. But the vessels pass through the defective areas. We are under the impression that, following treatment with vitamin D, the advance of the vessels is accelerated through those parts of the cartilage which previously had happened to become calcified as well as through the completely uncalcified portions. The peculiar slow degenerative changes and such phenomena as the "rejuvenation of the cartilage cells," described by Dodds and Cameron<sup>6</sup>, seem more easily explicable on the hypothesis of a chemical disturbance than on a solely mechanical one.

When lime salts deposit in healing rickets, the defect in the blood has already been rectified. The two phenomena, the restoration of a normal calcium-phosphorus equilibrium in the blood and lime salt deposition in the bone and cartilage, are indissolubly united in a cause and effect relationship. If one could produce calcification without altering the rachitic condition in the blood, in other words, if one could dissociate the two conditions, the determination which was the essential factor would be most simple. It is necessary to conclude that the mechanical hypothesis is capable of explaining the increased resistance of the cartilage and that the circumstantial evidence in favor of the chemical hypothesis is as yet too slight to establish its validity.

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## THE THERAPEUTIC USE OF VITAMIN C\*

GILBERT DALLDORF

THE therapeutic use of vitamin C means to me the treatment of scurvy for I know of no important uses of the vitamin other than the prevention of what are scorbutic manifestations. The relationship between the vitamin and scurvy is extremely intimate. The presence of the vitamin in the body tissues is simply the antithesis of scurvy. The action appears to be direct and certain phenomena of scurvy have even been observed *in vitro*.

In the past, scurvy was studied when it was prevalent, but our current interest in it is not due to its prevalence but to the stimulating work of the chemists in recognizing and identifying vitamin C. This has improved our methods of studying scurvy and influenced our conception of it. All of these things may best be reviewed by a brief chronological résumé of the past twelve years. If my review is too personal a record of events in which I have played a wholly unimportant part, please forgive me. An army of workers has tramped these roads and only a few have become familiar to me. Moreover I have seen all of the developments in the light of my own experience.

Our knowledge of scurvy was considerable before vitamins were discovered. Indeed scurvy was the first deficiency disease to be recognized as such. This happened one hundred and fifty years ago. It was experimentally produced and studied thirty-two years ago and was at that time the best understood of all the deficiency diseases.

So matters stood a dozen years ago. At that time Wolbach and Howe<sup>1</sup> published their beautiful anatomical studies of the experimental disease and shortly afterward a large, steady supply of scorbutic guinea pigs became available to me from the biochemical laboratories of Teachers College. There, as in many another laboratory, various foods were being assayed for vitamin content by feeding experiments. In the case of vitamin C the Sherman-LaMer technique was almost universally used. This consisted of feeding young pigs graded amounts of the vitamin during a test period of three months and diagnosing the effect by a gross examination of the animals. Fragility of the jaw, painful extremities, hemorrhages

\*Read February 2, 1939 at the Stated Meeting of The New York Academy of Medicine

in the muscles and the weight curve were the criteria used. It is interesting to recall that all of the important advances in the art of canning, so far as they relate to vitamin C, were gained through countless laborious experiments of this kind. Patient assistants went from cage to cage and tier to tier pipetting measured amounts of food stuffs into the mouths of reluctant guinea pigs.

Even at that time the most active searcher for the vitamin, Sylvester Soloman Zilva,<sup>2</sup> had observed that fresh fruit juices bleach indophenol. Only an unfortunate error, based largely on the wish to be as precise as possible, prevented him from recognizing that the reducing power of fruit juices, as measured by indophenol titrations, is due to vitamin C. However, the feeling seemed general in most laboratories that vitamin C would never be isolated because of its instability. Zilva's courage in undertaking a most unpromising line of research was widely acknowledged.

Zilva's observation of the indophenol reaction led to a chain of events which resulted in the isolation of vitamin C. In Frankfurt, Tillmans and Hirsch<sup>3</sup> adopted the indophenol method as a means of controlling the quality of fruit juices being sold in their city, a matter in which the civil authorities were interested. They discovered that only fresh juices gave the reaction Zilva described, not stale juice nor artificial juice. Tillmans suspected the significance of these results at once. Zilva had observed that when decitrated lemon juice was first oxidized with indophenol it remained potent, but that on standing it lost its antiscorbutic effect. He thought that the indicator was decolorized by a substance closely associated with the vitamin which tended to prevent its oxidation. Tillmans suggested the correct explanation, namely, that the oxidation was reversible and that the first stage of oxidation left the vitamin more prone to further oxidation than when in its original, reduced form.

Szent-Gyorgyi<sup>4</sup> had, the year following Zilva's study of the indophenol reaction, isolated a reducing substance from adrenal cortex and suggested its identity with the reducing substance described by Zilva in lemon juice. Within a few years the many similarities and the distribution of these substances became clear and Szent-Gyorgyi and associates in Cambridge and Waugh and King<sup>5</sup> in this country completed the chemical studies leading to our present knowledge of the vitamin. Thus occurred what we may consider to be the important contribution of our time to the story of scurvy.

During these years I was examining the tissues of guinea pigs and learning to recognize the scorbutic process. The material immediately suggested a rather interesting line of thought, for since the animals were as uniform as possible to begin with and all had been on the experimental diets for an equal number of weeks, they were naturally most suited to a study of the effect of various degrees of deficiency. This I endeavored to do and quickly discovered that I was able to recognize distinct anatomical effects of deficiencies which were never recognized clinically, even by individuals with long experience with the experimental disease. In other words, amounts of vitamin believed to be adequate for guinea pigs actually resulted in microscopic changes characteristic of scurvy. The amount of vitamin believed to be adequate for the prevention of scurvy had to be doubled to prevent certain skeletal lesions. From Sweden, Axel Hoyer,<sup>6</sup> at about this time, called attention to the sensitivity of the lesions in the teeth and demonstrated how they might be used in improving the biological assay methods and in shortening the test period. Because few biological chemists were prepared to make histological examinations, Celia Zall and I<sup>7</sup> developed a method whereby the rate of growth of the incisors of the animals could be measured and the growth rate used as a criterion of the degree of protection against scurvy. This proved still more sensitive to the effects of subclinical scurvy and showed that approximately three times the accepted protective amount was necessary to give maximum growth.

All of these methods were rendered obsolete before anything further was done with them by the chemical studies already mentioned and the wide adoption of the indophenol method for assaying vitamin C sources, a method which accomplishes in several minutes what previously had required three months. But to me the experience had served as a very impressive demonstration of the wide difference between clinical freedom from scurvy and optimal vitamin C nutrition. Many others reached the same position from different roads so that the growth of this idea occurred very quickly.

Our immediate impulse was to test the theory in man, and in many postmortem examinations since then I have searched for manifestations of scurvy. It was therefore not surprising to me when several years ago Park<sup>8</sup> reported a surprisingly high incidence of both radiographic and anatomic evidence of scurvy in 125 children studied thoroughly with scurvy and rickets in mind. Scurvy may be found, both clinically and

anatomically, if the search be thorough—evidence, no doubt, that many of our people still live on the borderline of vitamin C deficiency. But the search went on for clinical criteria of this mild form of scurvy. The progress of these studies in the years immediately preceding the discovery of the vitamin was based on studies of the capillaries. The capillary resistance test was first tried on scorbutic guinea pigs and later applied to apparently healthy individuals. This showed that the incidence of capillary fragility was surprisingly high, approximately 30 per cent among certain groups.

The capillary test, especially as performed with a tourniquet, is of course familiar to all of you. Hess,<sup>9</sup> years before my own experience, had used it to advantage in studying what he called latent scurvy and more than a generation earlier rather similar observations were made by Auspitz<sup>10</sup> while cupping patients.

Everyone who has used the test has learned to regret its variability and inconstancy and to deprecate its diagnostic value. Hess, however, found it distinctly positive in most cases of scurvy and we believed the average value in large groups of individuals might be still more reliable. Thus we hoped to learn about the adequacy of the vitamin C intake of different economic groups. It was also evident that capillary fragility was diagnostic if a prompt response followed specific therapy. Furthermore it was generally agreed and had been the experience of many generations of medical men that the hemorrhagic diathesis was the most characteristic manifestation of scurvy. We might expect capillary changes to be the first and most delicate manifestation of scurvy, so there existed some tantalizing reasons for treating the capillary test seriously. At any rate, many studies were made with it which showed a large part of the general population to have fragile capillaries with a rough agreement between vitamin C intake and the level of the resistance. In my own laboratories these results were supported by feeding experiments in which extracts of human tissues from the postmortem room were assayed biologically and vitamin deficiency demonstrated to be common in this way.

But soon the chemical methods were introduced and displaced the capillary test. Interestingly enough, they have also shown approximately the same incidence of partial starvation of vitamin C as the capillary tests did but the proponents of one test seldom find individual agreement between the two techniques.

The weakness of the chemical method has been that it does not of



TABLE I  
CHEMICAL AND CLINICAL TESTS FOR SCURVY

	<i>Fasting Blood (Mgs per cent)</i>	<i>Capillary Resistance (Cm Hg neg pressure)</i>	<i>Urinary Excretion following a test dose (Mgs)</i>
Normals	0.80	45	44.0
Subclinical Scurvy	0.36	29	24.0
Severe Scurvy	0.064	5	2.0
Peptic Ulcer with Hemorrhage	0.33	11	8.0
Nonscorbutic Hemorrhagic Diseases	1.27	22	58.0

(With the exception of the case of severe scurvy the values are given as the averages for small groups of patients)

itself demonstrate at what level of saturation or blood concentration of vitamin, deleterious effects occur. There have, it is true, been a few observations of associated gingivitis, but little of much weight. Most of these studies have been made by biological chemists with poor facilities for clinical observation.

Sloan and I<sup>11</sup> studied cases of manifest scurvy, mild or doubtful scurvy and normal individuals by all of the suggested methods including the capillary test. It was found that the fasting blood level, of all the single, simple procedures, furnishes the best evidence of vitamin C nutrition. Only the blood curve following a test dose is more precise. The total urinary excretion during twenty-four hours is frequently misleading although the excretion curve during the six hours following a test dose and even the total excreted vitamin during that period are fairly reliable. It was also found that the capillary test was as a rule positive in those individuals showing partial saturation. I have summarized the results from what we considered the best tests in Table I.

In general they conform with the experience of others. Several things may be learned from them. The fasting blood level clearly mirrors the condition of these individuals and nicely distinguishes between the frank scorbutic, the subclinical scorbutic and the normal. The capillary resistance test does likewise but is misleading in two groups. In the cases with ulcer, two-thirds of the patients gave false negative results, presumably because they were so exsanguinated that their superficial vessels were empty of blood, and rupture, if it did occur, could not be recognized.

The nonscorbutic group of hemorrhagic diseases, including a case of thrombocytopenic purpura, gave false positive results. In the first group, once relief was afforded the anemia, more revealing capillary tests were secured and these improved under vitamin treatment. In the second group no change followed treatment.

The table seems to me to serve two purposes. In the first place, the definite association of capillary fragility with degrees of unsaturation believed to be abnormal, constitutes definite objective evidence that the condition of subclinical scurvy has at least one morbid manifestation. This can be correlated with the observations already mentioned to constitute a continuous chain of evidence indicating that such degrees of deficiency are actually degrees of scurvy and not within the normal range. But much more will be required to be certain of this most fundamental point. The second use of the table is that it illustrates the methods by which vitamin C absorption, storage and excretion may be studied.

Nutrition is properly a major concern of our public health services. But there is a field of pathological deficiency in nutrition which is wholly within the practice of clinical medicine. Thus you may recall in the first of my tables the low blood concentration of vitamin C and the low urinary excretion of a small group of cases of peptic ulcer complicated by massive hemorrhages. Table II contains other information on one of these patients. You will note that coincidental with saturation, the bleeding stopped. We have seen various cases of this kind and most of these proved to be deficient in vitamin C. This is representative of the applications we can make of our newly acquired knowledge.

There are various other similar conditions. Almost all of these seem related to known facts concerning scurvy. For example, the healing of surgical wounds may be hindered by vitamin C depletion. There is no doubt that this does occur experimentally. The issue at present is solely whether a sufficient degree of deficiency occurs in our surgical clinics to prevent union. Several writers have found cases which suggest this. The product of fibroblasts, collagen, does not form in the absence of vitamin C either *in vivo* or *in vitro*. Therefore any condition in which defective scar tissue occurs might well be held suspect, just as idiopathic hemorrhage should suggest scurvy. The laboratory can supply evidence of value, as I have shown, and the therapeutic test is usually conclusive.

Various such peculiar manifestations of scurvy are secondary in nature. Thus the ulcer patient may be presumed to have faulty absorption

TABLE II

USE OF VITAMIN C IN A CASE OF PEPTIC ULCER  
WITH HEMORRHAGE

Day	*Urinary Output in Vitamin C		Vitamin C Intake (mgs)	Blood vitamin (mgs %)	Blood in stool	Blood	
	in 6 hrs (mgs)	in 24 hrs (mgs)				Hgb (%)	RBC (mil)
1					4+	32	097
2						33	24
5					4+	52	
13					4+	53	30
22	18 (4%)	11	1000				
23	30 (6%)	54	500				
24	52 (10%)	65	500		1+		
25	134 (27%)	125	500	0.50		65	38
26	210 (40%)	156	500				
27	201 (40%)	202	500				
28	238 (48%)	225	500	1.05	2+	69	40
31-35			oral		—		
75	698 (70%)	702	1000	1.10	—		
92			oral	0.95	—		
115			oral	1.07	—		

(The lower values of excreted vitamin C in the twenty-four hour period represent losses incidental to storage overnight)

although some are probably depleted by too restricted diets. The presence of a serious disease in no way minimizes the requirement, the insistent requirement, for the vitamins. Thus infectious diseases increase the requirements. Factors such as activity and physical exertion are important. This is by no means a new observation. The old sailing captains complained that their best, most energetic seamen were the first to be incapacitated by the scurvy, the loafers suffered last.

These are but a few of the possibilities which must be explored in explaining the unexpected cases of vitamin C deficiency. The rule we have followed has been to suspect deficiency in all cases of hemorrhage and musculo-skeletal weakness. All such patients are tested. A number

\* Urinary output expressed in mgs. and percentage of intake

are found who seem to be truly depleted and who benefit from specific treatment

Finally, a few words concerning treatment. The vitamin may be given in the crystalline form, as tablets, or intravenously. It may be given in food. There are occasions when each method has advantages. The severe scorbutic deserves large doses of the pure substance as well as a model diet. This is true because severe scurvy is a dangerous condition, the depletion is severe and the equivalent of two or three liters of orange juice may be given in a single 10 cc dose of crystalline vitamin C. Similarly the patient with severe hemorrhage should be given one or two large doses. A large dose is 500 or 1000 mgs. We have used 1000 mgs as a rule but I believe that 500 mgs is probably sufficient. Indeed it may be that 100 mgs will accomplish as much, I do not know. Since the vitamin is nontoxic we have inclined to give large doses. We have never seen a reaction to such dosage. Our practice is to give a gram or a half gram daily.

In the mild scorbutic the vitamin is administered parenterally, if the case suggests faulty absorption or abnormal requirements, and as part of the therapeutic trial, always an illuminating matter. The treatment otherwise is dietary. The prescription of vitamin tablets would seem to have a very limited usefulness.

The use of vitamin C in pills containing all of the known vitamins and as a prolonged substitute for a correct diet appears to be a serious mistake. In the first place the stability of the vitamin in natural sources is infinitely greater than in the pure form. Twenty-five years ago Funk remarked on the stability of vitamin C in lemon juice where it withstands heating to 110 degrees. Buffers present in fruit juices are protective probably within the man as well as outside him. In the second place, the natural sources contain other vitamins, minerals and probably many wholly unrecognized factors of advantage. Thus several careful workers have demonstrated that supposedly pure but extracted vitamin C had attributes not present in the synthetic preparations. We have yet to recognize all of the vitamins if indeed we ever shall be able. The shotgun vitamin pill is therefore not a substitute for a proper diet. It is also unsound because those individuals able to afford such treatment usually do not need it while those who might be benefited are unable to buy it. A dollar will buy more vitamins in the market than in the drug store.

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## THE USE OF TETANUS TOXOID IN PRIVATE PRACTICE\*

ROBERT PAGE ROGERS

IT was a very logical step after the development and successful use of diphtheria toxoid to attempt similar work with tetanus toxoid. Let us first review some of the important steps by which this present knowledge has been reached. We owe a great deal of the progress to Ramon<sup>1</sup> and his co-workers at the Pasteur Institute. Attempts were made by others even earlier. Eissler and Loewenstein in 1915 used a formalized toxin with no success. Valle and Bazy employed toxin treated with Gram's iodine solution. Two out of seven cases had some specific antitoxin created thereby. Ramon,<sup>1,2</sup> stimulated by his brilliant work with diphtheria toxoid, prepared a formalized tetanus toxoid which he gave in three doses: 1 cc., 1.5 cc., and 2 cc. at three week intervals. He obtained an immunity in his series, measured by blood neutralizing tests, of from 1,000 to 3,000 lethal doses, i.e., one to three units. One cc. of blood will protect a guinea pig against 1,000 to 3,000 lethal doses. A fact of very great significance which he discovered is that the acquired reactivity persists, so that a later dose rapidly raises the titre.

In 1933 he<sup>3</sup> reported thirteen cases which had received on an average of three injections in 1927-28. These titrations were made in 1931-32, i.e., about four years after the immunizations. One cc. of serum protected against from 4 to 300 lethal doses, the average being around 60 or about 1/20 unit. Ramon<sup>4</sup> further reported in 1937 two individuals, one immunized eight years before, the other nine years previously, possessing 1/200 units titre, which he believes sufficient for protection. In eight days after the boosting dose one of these individual's serum rose to more than one unit.

It is now a law in France that antitetanus immunization is to be given to all soldiers. In 1936 over 400,000 were vaccinated. A boosting dose is to be given every five years. They are using the formalized preparation

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Reactions have been very slight. The immunity appears significantly after the second dose.

At this point, the work of these French scientists on the use of combined vaccination should be considered. In testing the titre of horse serum in horses that he was immunizing, Ramon<sup>5</sup> noted that the serum of some horses seemed to have a spontaneous increase in titre. On closer examination he found that these horses had abscesses or inflammation at the site of injection. The use of some foreign material injected along with the immunizing dose suggested itself. He first tried tapioca and found that this raised the resulting titre considerably. Then he tried associated vaccinations with similar results. Sacquepée and Jude<sup>6</sup> found that in a small series one month after the third dose of combined diphtheria, typhoid and anti-tetanus injection, 98 per cent had more than 1/30 unit.

In this country Jones and Moss,<sup>7</sup> and Cooke<sup>8</sup> have written concerning the use of combined toxoids. The routine procedure at the St. Louis Children's Hospital and Washington University Children's Clinic is now two injections, two months apart.

To return to a consideration of the plain tetanus toxoid, in this country Lincoln and Greenwald<sup>9</sup> made observations on nineteen patients who were given three doses of tetanus toxoid (formaldehyde) at weekly intervals. They had no general reactions and only slight soreness locally. One child developed no immunity, the others developed appreciable amounts. Bergey and Etris<sup>10</sup> demonstrated that the alum precipitated toxoid gave a level higher than one immunizing dose of 1,500 units of antitoxin. Since then Sneath and Kerslake,<sup>11</sup> Jones and Moss,<sup>7</sup> Boyd,<sup>12</sup> Hall,<sup>13</sup> Gold<sup>14</sup> and others have confirmed this work of Bergey and Etris.<sup>10</sup> A comparison of the results obtained by different workers is shown in Chart I.

Let us now consolidate and evaluate this knowledge and determine to what conclusions it leads us. First of all, what is the minimum protective blood level? From several sources we know that after 1,500 units of antitoxin the blood level rises to between 0.1 unit and 0.25 units within twenty-four hours to forty-eight hours and remains about that level gradually falling so that at the end of two weeks there is practically no protection. Sneath<sup>15</sup> showed that when guinea pigs were injected with a mixture of tetanus spores and 50 per cent calcium chloride solution, unimmunized guinea pigs all died of tetanus within forty-eight to seventy-two hours, but that if these pigs had been immunized and their blood

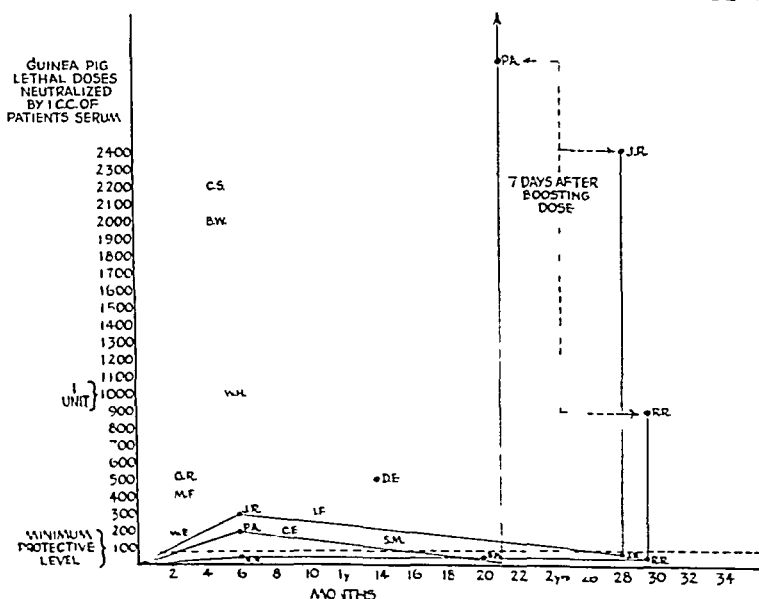
CHART I  
COMPARISON OF RESULTS OBTAINED BY SEVERAL WORKERS

Antitoxin Units in 1 cc of Blood	Formol Toxoid				Alum Precipitated Toxoid			
	Ramon and Zoeller (1933) (a)	Sacquepee (1933) (b)	Hall (1937) (c)	Sneath and Kerslake (1934) (d)	R A W College (1936) (e)	Bergey and Ltriss (1936) (f)	Gold (1937) (g)	Hall (1937) (h)
0.01		3		3				
0.01 to 0.1		107	11	6	3		1	
0.1 to 1	Most cases	126	1	20	21	14	13	12
1 and over	A few cases	1			6	16	4	1

- (a) Exact numbers not quoted 1st dose, 1 cc, 2nd dose, 30 days later, 1.5 cc, 3rd dose, 10 to 15 days later, 1.5 cc, tested about 1 month later
- (b) 1st dose, 1 cc, 2nd dose, 20th day, 2 cc, 3rd dose, 30th day, 2 cc, tested about 6 months later
- (c) 1st dose, 1 cc, 2nd dose, 6 weeks later, 1 cc, 3rd dose, 2 weeks later, 1 cc, tested 6 weeks after 3rd dose
- (d) Dosage and test as in (a)
- (e) 2 doses of 1 cc at intervals of 6 to 7 weeks Tested about 1 month later
- (f) 2 doses of 1 cc of alum precipitated toxoid separated by an interval of some months Tested 1 month after 2nd dose
- (g) 2 doses of 1 cc of alum precipitated toxoid at intervals of 92 days Tested from 7 to 15 days after 2nd dose
- (h) 2 doses of alum precipitated toxoid at an interval of 6 weeks Tested about 6 weeks after 2nd dose

CHART II

IN CHART II ARE SHOWN THE PROTECTIVE LEVELS REACHED IN FOURTEEN PATIENTS AFTER ADMINISTRATION OF TETANUS TOXOID



Protective levels reached in 14 patients (12 of whom are allergic individuals) after two 1 cc doses of alum precipitated toxoid given two months apart, the curves are approximate immunity curves for 3 cases



titre showed 0.01 unit or more, 87 per cent remained completely protected and 13 per cent showed mild tetanus from which they recovered. A group of mice showing 0.1 unit or more were completely protected against 100,000 spores. It would seem then that 0.1 unit is a safe minimum level to accept and is probably much larger than is necessary to protect against infection resulting from trivial wounds. Whether this level is sufficient for protection against massive infection is not known.

What dose and what spacing of doses should be used to produce the minimum level? It is generally conceded that the alum precipitated preparation should be used. The reactions are few and very rarely general, usually local soreness with very little discomfort. Two 1 cc doses given sixty to ninety days apart appear to give the highest titre. Usually about seven to ten days after the second dose the titre has risen to over 0.1 unit per cc even if this second dose is given as long as two years after the first dose. We may say that very adequate immunity then develops certainly by fourteen days after the second dose and in most cases by seven days.

How long does the active immunity last at the minimum protective level or above?<sup>16</sup> It varies considerably. It has disappeared within ninety days after the second injection and has lasted as long as two years. The basal immunity upon which a secondary stimulus may be had is probably lifelong.

A crucial question is, whether the boosting dose given months or years later, after the level in the blood has fallen to well below the accepted minimum protective level, will be effective. In America there is now ample confirmation of Ramon's work. Hall,<sup>13</sup> from his studies in the Navy, concluded that no matter what interval was used in the basic courses or how low the level of antitoxin at the time of the final or secondary stimulus, the antitoxin titre rose in seven days or less to highly effective levels. In one week after a boosting stimulus given one year after the immunization, Jones and Moss<sup>7</sup> found that all but one had a blood level comparable with that following the old prophylactic injection. These results are analogous to those published by Sneath and Kerslake.<sup>11</sup>

Cowles<sup>17</sup> at Yale endeavored to find out just how quickly his boosting dose acts. Twelve men immunized one year previously and having titres ranging from 1/50 to 1/5 unit of antitoxin per cc received 0.5 cc of alum precipitated toxoid subcutaneously. Six of these when tested on

the third day after the toxoid administration failed to show any significant increase in titre, of eight tested on the fourth day, four responded, of eight tested on the fifth day, all had  $1/20$  unit of antitoxin or more. By the seventh day all had reached  $1/2$  unit or more with the exception of one man who had only  $1/20$  unit. The duration of this higher immunity after a repeat dose is not known. Gold<sup>14</sup> states that it may fall below  $1/10$  unit in three to six months. According to Sneath and Kerslake<sup>11</sup> a secondary stimulus of plain toxoid seemed to produce a more lasting immunity. Further work must be done on this point.

Certain theoretical considerations should be mentioned. It seems reasonable to believe that, given a certain immune level induced by active immunization, this level would be raised by the stimulus of an active infection. A person whose immune mechanism was set to combat tetanus by previous active immunization would show a rapid response to the production of toxin by the infection, just as that same person would show a rapid rise in immune level as the result of a boosting dose of toxoid. This type of response would occur, we assume, provided that the infection produced enough toxin to leave some toxin free and unneutralized by antibodies already existing in the body. Wolters and Dehmel<sup>18</sup> showed that guinea pigs can react this way. They inserted into immunized animals splinters infected with tetanus spores and found that these animals did not develop tetanus but did show appreciable elevation in protective titre. We can reason also somewhat by analogy from immune reactions in individuals previously immunized against diphtheria. There is some evidence to show that the amount of toxin in a Schick test is sufficient to stimulate increased antibody production. More work needs to be done to confirm this very important matter.

### CONCLUSIONS

We may now ask what facts are well enough substantiated to rely on? How far may we apply them?

It has been shown that two doses of 1 cc each of alum precipitated toxoid given two or three months apart or three doses of plain toxoid 1 cc, 1.5 cc, 2 cc at three week intervals will in seven, at the outside fourteen, days after the last dose produce a blood level as high or higher than 1500 units of the old antitoxin. A boosting dose given one to several years later will bring this level back to a protective level and often far above in seven days in almost every case tested.<sup>19 20 21 22</sup> The reactions

to these toxoids are slight. The alum precipitated toxoid is quite thermostable and therefore keeps well.

To be able to rely absolutely on immunization by toxoid the following things should be done:

1. A blood titration test should be made two months after the last immunizing dose (laboratories are now equipped or can soon be equipped to do this).
2. If injury requiring protection occurs any time after three months after immunization, a boosting dose should be given within twenty-four hours of injury.
3. Even this should not be relied on in cases of very extensive injury such as would require gas bacillus prophylaxis or injuries where there was extensive hemorrhage. In these cases antitoxin should be given also.

Tetanus rarely develops before five days but it is in this type of case that the incubation is likely to be early. The usual incubation is between seven and fourteen days.

Who *should* receive active tetanus immunization?

1. First of all I place those who are sensitive to horse serum. That means, of course, those who have had severe and moderate serum reactions from previous serum injections.
2. Asthmatic patients.
3. Other allergic individuals if they are in occupations or indulge in avocations that carry with them danger of injury.

It is justifiable to give tetanus immunization to the following optional groups:

1. Children, especially those living in the country or those who ride. Statistical analysis shows that most of the cases of tetanus at present occur from trivial injuries. These cases would very definitely be prevented by such prophylaxis whether a blood titration was made or not.
2. Individuals, non-allergic, engaged in hazardous occupations or avocations.

The author is greatly indebted to Mr. Charles K. Greenwald, Bureau of Laboratories, New York City, for doing the laboratory work on the cases reported.

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## THE INFLUENCE OF EMOTIONAL FACTORS UPON PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES\*

FRANK FREMONT-SMITH

THE increasing pace at which new knowledge in the basic sciences is being applied to the solution of clinical problems, together with the widespread demand for health-care by a public better informed than ever before, has created new and urgent problems for medical education and for medical practice. As we survey the present situation in an effort to foresee changes in the teaching and practice of medicine which the future must surely bring, we may well ask whether in the swiftness of our advance we may not have lost something of the wisdom of the past, whether the new and revealing laboratory techniques have not focussed attention too exclusively upon organs and parts of organs to the neglect of the whole, upon disease processes to the neglect of the individual who is diseased. Francis W. Peabody<sup>1</sup> said "What is spoken of as a 'clinical picture' is not just a photograph of a man sick in bed, it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes and fears." And Hippocrates<sup>2</sup> before him taught that "the nature, even of the body, can only be understood as a whole." Is there something in this philosophy which is not included in the modern approach to medicine? Was a better knowledge of the whole perhaps the secret of the much mourned family physician who in the course of years came to know the life history of his patients and of their families and could evaluate the present illness in the light of such perspective?

That the medical profession is becoming increasingly aware of this question is evidenced by the frequency with which the medical student is admonished to look upon the patient "as an individual" and view him "as a whole." But unless this viewpoint is applied in fact to the individual patient, it becomes a mere abstraction with little meaning at the bedside,

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where we are too apt to focus the best laboratory procedures on the depersonalized "case"

Is not the public, nearly all of whom sooner or later become our patients, beginning to feel a certain dissatisfaction with modern medical practice, even when skilled specialists are available to study the dysfunction of this organ or of that, and physical examinations and laboratory tests are far more revealing than in the past? Why is it that a viewpoint, accepted by the ancients, sensed by the country doctor, and enunciated by the present leaders of our profession, should still elude us in daily practice? The answer lies partly in the inadequacy of the technique of history taking, to which we shall return later, and partly in the focus of the physician's interest. To the family doctor the patient is usually no stranger when he seeks advice. Often the physician has known him since childhood, and quite naturally takes into consideration his previous illnesses, personality and family background, so that the patient's symptoms are seen in the perspective of the life history of the individual. The modern physician, on the other hand, rarely sees the same patient through the years. With many technical devices at his command, he tends to become preoccupied with the function of organs and organ systems which can be measured with ever increasing accuracy. But this alone does not satisfy the patient whose primary interest is in himself — the sick man.

It is not my purpose to discuss the need of studying the individual patient, his emotional tensions, peculiarities and prejudices, in order merely that we may know how best to gain his confidence, nor merely that we may deal with overt emotional crises or be ready on occasion to play the role of father confessor. There is another more cogent reason why the modern doctor, whether he be general practitioner or specialist, can no longer afford to overlook the personality pattern and emotional responses of the individual patient. For in the patient's personality structure, in his way of reacting emotionally or of failing to react to his environment are to be found the factors which not only lie at the root of the so-called "functional" disturbances but which also often determine the onset, severity, duration, exacerbations, and even the outcome of disease.

The physician today is not satisfied with the diagnosis when, in the case of an infectious disease, the infecting agent has been identified. He wants to know both the source of the infection and the nature of the immunological disturbance which made infection possible. We have

progressed beyond the stage where simple cause and effect relationships are sought. The biochemical changes taking place in the patient are as important as the nature of the invading organism for the production of disease. Similarly, when a gastric ulcer has been accurately described by x-ray and gastroscope, the diagnosis should be considered still incomplete until we have investigated the factors which lead to exacerbations of symptoms and threaten hemorrhage or perforation. If the symptoms are accentuated by family quarrels, this fact should be included in the clinical picture. Its neglect may prevent a cure. If hospitalization of an ulcer patient is more effective because it removes the patient from the scene of the quarrels than because it allows strict regulation of the diet, this also should be understood by the physician. Obviously in such case, proper therapy must include either a change in the home situation or in the patient's attitude toward it.

In order to understand how emotional factors can influence the process of disease it will be helpful to review briefly the anatomical, physiological and biochemical mechanisms which are normally activated during emotional stress. Walter B. Cannon<sup>3</sup> in his classic studies on emotional excitement has shown clearly the profound changes occurring in animals during rage and fear, i.e., the elevation of the blood pressure, the diversion of the blood flow from skin and splanchnic regions to muscles, heart and brain, the inhibition of gastric function, the pouring into the blood of glucose, and of adrenalin — all evidences of pronounced activity of the sympathetic division of the autonomic nervous system. Recently Morris Bender,<sup>4</sup> while working in John F. Fulton's laboratory at Yale, and now at the Mount Sinai Hospital, has presented evidence that acetylcholine as well as adrenalin is secreted into the blood in cats and monkeys during fear, showing that the parasympathetic as well as the sympathetic division of the autonomic nervous system may be thrown into activity during emotional excitement. This evidence of parasympathetic action fits in well with a number of clinical phenomena, as indicated by Kling,<sup>5</sup> such as blushing, lacrimation, fainting, vomiting, involuntary urination or defecation, any of which may occur under intense emotional stress, and which cannot be readily understood on the basis of sympathetic stimulation alone.

Since the autonomic fibers are widely distributed throughout the organism to skin, blood vessels, viscera, reproductive system, special sense organs, kidneys, the glands associated with the gastrointestinal

tract and the endocrine glands, which pour their secretions into the blood stream and thus influence distant organs, it is evident that activity of the autonomic nervous system, either directly or through the mediation of the blood stream, may be expected to have an influence upon the function of practically every organ and tissue. There is no valid reason why a diseased organ should escape such influence, on the contrary there are striking examples of pathological states which render an organ oversensitive to autonomic stimulation. For example, in Raynaud's disease the blood vessels of the affected part become overresponsive to sympathetic stimulation, while in hyperthyroidism the heart, as well as other tissues, overreacts to adrenalin injection as well as to emotional stimulation.

The autonomic nervous system has intimate connections with the central nervous system on both the efferent and afferent side. Recent studies, admirably reviewed in Fulton's<sup>6</sup> *Physiology of the Nervous System*, have made it evident that the hypothalamus is the chief center for the integration of impulses to and from the autonomic system, and that intimate connections exist between the hypothalamus, the thalamus and the cerebral cortex. Stimulation\* of the posterior and lateral nuclei of the hypothalamus in animals produces diffuse discharge of all divisions of the sympathetic system, causing acceleration of the heart, dilation of the pupils, inhibition of peristalsis of the gastrointestinal tract, pilomotor activity, rise in blood pressure, increase in respiratory rate and decrease in bladder tonus. Stimulation of the middle nuclei, however, results in responses of an opposite type, being in general characteristic of parasympathetic activity. Thus the heart rate is slowed and the auriculoventricular conduction time is increased, there is increase in peristalsis of the stomach, and increase in tonus of the bladder. A fall in blood pressure can be produced by stimulation of the anterior region of the hypothalamus. That these two types of response to stimulation of the hypothalamus are mediated by the sympathetic and parasympathetic nerves respectively is proved by the fact that the appropriate responses cannot be obtained after section of sympathetic, or of parasympathetic nerves, as the case may be. Experimentally produced lesions in the hypothalamus lead to disturbances of heat regulation, of water regulation, of carbohydrate and fat metabolism, and of sexual function. Finally, the outbursts of rage which occur spontaneously or are readily elicited in animals after

\* For references to this and the following experiments on the hypothalamus and the cortex, see Fulton.<sup>6</sup>



decortication disappear when the posterior area of the hypothalamus is destroyed. These pseudoaffective outbursts, called "sham rage" by Cannon and Bard, are accompanied by signs of widespread sympathetic activity, indicating the intimate relation between affective discharge and activity of the autonomic nervous system.

The release of exaggerated emotional expression and autonomic activity by decortication implies a cortical inhibition or regulation of these functions but, as Fulton<sup>6</sup> has said, it is only within the last few years that the extent to which the cerebral cortex influences the autonomic nervous system has become obvious. In the cat and monkey, stimulation of discrete areas of the cortex will evoke marked elevations in blood pressure, while stimulation of neighboring areas results in a fall in pressure. The rise in pressure is accompanied by acceleration of the heart, while the decrease in pressure is associated with slowing of the heart rate. These responses demonstrate both a sympathetic and a parasympathetic representation in the cortex, since the rise in blood pressure and increase in heart rate are diminished although not wholly abolished by section of the splanchnic nerve and removal of the stellate ganglia on both sides, while section of the vagi abolishes the lowering of blood pressure and the slowing of the heart.

As further evidence there may be cited the experiments of Green and Hoff<sup>7</sup> on cats and monkeys which indicate that in the motor and premotor areas of the cerebral cortex there exists a mechanism for diverting the blood from visceral to muscular bed, which is mediated through the peripheral nervous system. Thus stimulation of the cortex may produce physiological changes analogous to those which occur spontaneously in rage or fear. Stimulation and ablation experiments have demonstrated the cortical control of sweating, as well as the absence of the psychogalvanic reflex on the contralateral side when a sharply localized area of the cortex is removed. Dilation or constriction of the pupil, as well as lacrimation and salivation, may be provoked by cortical stimulation. Ablation of the frontal lobes produces motor hyperactivity of the stomach with pyloric spasm, while stimulation of the frontal cortex also influences gastric peristalsis. The "psychic" flow of gastric juice is dependent upon cortical function, and micturition is also partly under cortical control.

Thus we may make a rough sketch of the intricate organization of the autonomic nervous system, its integration in the hypothalamus and

regulation in the cerebral cortex where there exist both sympathetic and parasympathetic representation. The organism is prepared for instant and violent action and yet so regulated that whether at rest or in action, its internal environment is kept within those limits of relative constancy which are essential for efficient activity and even survival.

The inward nature of affective experience still eludes us. The James-Lange theory of the emotions has been discarded, and a satisfactory formulation will probably have to await more precise information on both the clinical and experimental side. It may be stated, however, that affective states, although often evoked by sensory stimuli, are dependent primarily upon central rather than upon peripheral activity, that the gross patterns of emotional expression are organized subcortically, since decortication leads to their release in exaggerated form, and finally that the pathways for such nervous discharge are via the hypothalamus into the autonomic nervous system. The ultimate action of the autonomic nervous system, and hence of emotional activity, upon the tissues of the body is brought about by the chemical mediators adrenalin and sympathin released by sympathetic stimulation, and acetylcholine released by activity of the parasympathetic nerves and probably by other hormones, whose secretion or discharge into the blood stream may be influenced by activity of the autonomic nervous system. Since adrenalin and acetylcholine, both highly active physiologically, may be found in the blood stream simultaneously under fear reactions, and since fear may be accompanied by symptoms due to sympathetic or parasympathetic activity, or both, it seems probable that the sympathetic and parasympathetic divisions are stimulated nearly simultaneously in the homeostatic regulation of the organism. Whether the symptoms resulting from emotional stress are predominantly sympathetic or parasympathetic may then depend either upon the relative intensity of the stimulation of these two divisions, or upon hyper-reactivity of an organ or tissue. Among the causes of such local hyper-reactivity are various pathological processes. Such is the system, anatomical, physiological and biochemical through which emotional activity is expressed.

In Dunbar's volume, *Emotions and Bodily Changes*,<sup>8</sup> there is reviewed a vast but scattered literature dealing with these psychosomatic problems. Here may be found many striking case histories illustrating the influence of emotion upon disease, cases involving nearly every organ of the body. Almost every physician with whom this topic is

discussed will remember one or two dramatic instances. As Dunbar points out, however, few systematic studies have been made. Until this is done, using effective diagnostic methods, we cannot know how many such cases are being missed.

One important reason why the role of emotional factors is overlooked in many cases is because in history taking we assume that the patient will remember accurately and thereby ignore the power of his "forgettary" (Wile<sup>9</sup>). We are inclined to think of remembering as an active process and tend to overlook the fact that we could not focus our memory upon an incident or object unless we had an efficient mechanism for excluding at that moment all the other memories which might crowd in upon us. Forgetting often must be looked upon as an active process, not just an absence of remembering. In fact the vigor with which we are able to forget is at times appalling!

It is common knowledge that when an old memory is revived by some appropriate stimulus, not only is the original experience remembered, but the emotions associated with it are also reawakened and felt, often with intensity. What is less well known, but even more important for the physician, is the fact that the stimulus may sometimes fail to bring to conscious memory the old experience, and yet reawaken the emotional feeling and the concomitant activity of the autonomic nervous system. Under such circumstances the individual may realize that he is frightened or angry but wrongly attribute the feeling to something in the present situation, failing to realize that its source is in an only partially awakened memory.

In some instances of partly evoked memories, the emotion may not be recognized as such, only the symptoms due to autonomic activity coming into consciousness. The individual notices a pounding of his heart, or perhaps feels nauseated and vomits, but remains unaware of fear in the first instance, or of disgust in the second. If the heart, digestive system, or any other organ is especially sensitive to autonomic activity, or is already the site of disease, then it is not difficult to see how the arousing of emotional tension, can lead through activity of the autonomic nervous system to serious symptoms and to the extension of the pathological process. For instance, a patient with a chronic peptic ulcer had three severe hemorrhages from the ulcer each occurring within twenty-four hours of an emotional crisis. Here may be cited also the recent observation of Bruenn<sup>10</sup> that anxiety causes an increase in the auriculo-

ventricular conduction time, as shown by the electrocardiograph, in patients with rheumatic fever

Since the patient has often completely forgotten the information needed by the physician to determine the importance of emotional factors in the illness, or if he remembers the disturbing factors, has forgotten their association with the onset of symptoms, the direct question-answer technique of history taking will almost inevitably fail to reveal the emotional tension or its relation to the illness. The patient cannot be expected to tell what he has forgotten, what, because of its disturbing nature, has been excluded from conscious memory. But since anxiety in one form or another is usually at the root of evasion or of repression of emotional problems, an essential factor in aiding the patient's memory is the establishment of confidence in the doctor.

In the presence of disease, how can we determine whether emotion plays a significant role? The diagnosis of "functional disturbances" formerly was made by exclusion of discoverable organic processes, but this is both difficult and inadequate. Moreover, the arbitrary distinction between "organic" and "functional" is more misleading than useful. We need criteria for the positive diagnosis of the role of emotion in illness. Among such criteria is a time relationship between an emotional crisis and the onset of symptoms. The positive diagnosis is considerably strengthened if several exacerbations of symptoms, or attacks have been immediately preceded by recurrence of the same or similar emotional conflicts. If the patient fails to recognize any connection between the emotional tension and the symptoms, and particularly if the patient has completely forgotten the emotional crisis or its time relationship to the onset of the symptoms, then the role of the emotion as an etiological factor in precipitating the symptoms is rendered highly probable.

The intellect is expected to govern the emotions, the cerebral cortex to regulate the activity of the lower centers, but intellect is often powerless before emotions which have been forgotten, for the lower centers may then discharge with an uncontrolled intensity, and often with a stereotyped pattern, which is reminiscent of the behavior of the decorticated animal.<sup>11</sup> This suggests that the exclusion from consciousness of the memory of an emotionally disturbing event may be analogous to a partial temporary decortication. In such circumstances the return to conscious memory of the forgotten experience may lead to an abrupt decrease in activity of the autonomic nervous system and prompt

cessation of the accompanying symptoms

This sequence of events was reproduced in man by F Deutsch and E Kauf<sup>12</sup> in 1923, who set out "to show experimentally that ideas and experiences originally accompanied by anxiety but long since forgotten, are the cause of disturbances in the cardiovascular system" I quote from Dunbar's review<sup>8</sup> of their article

" 'An exciting experience was suggested to the subject in hypnosis, with the simultaneous suggestion of complete amnesia for it Furthermore, the posthypnotic suggestion was given that with a certain signal (seemingly accidental showing of a handkerchief) the subject would have the same sensations as during the experience When, after hypnosis, the handkerchief was shown, there was in all cases a definite increase in pulse rate (maximum 27 beats per minute), similar to that during the suggestion of the experience in hypnosis ' This shows, the authors say, that an experience which is no longer in consciousness may produce the same sensations as at the time of its first happening \* \* \* Two subjects were given, in addition, the suggestion that on the dropping of the handkerchief they would remember the experience completely Whereas on production of the handkerchief there were pulse accelerations of 15, 12, 13 beats per minute in one case, 22 and 27, in the other, repetition of the stimulus after dropping of the handkerchief produced no, or only negligible, acceleration Especially in one case there was intense anxiety with recollection of the experience "

These experiments illustrate that an emotionally disturbing experience induced and forgotten under hypnosis on awakening may lead to exaggerated response when partially reactivated In a similar way an individual with pent up but unrecognized anxiety may be thrown into a state of terror by an experience, such as a barely-avoided automobile accident, which would ordinarily evoke but slight fear The resulting terror, which may persist for some time, is absolutely real to the individual and may cause him to misjudge the actual danger in the present situation In some cases only a very specific stimulus, one closely connected with the forgotten experience, is able to release the repressed emotion In other instances, as in a vivid radio broadcast at a time when war seemed imminent, widespread panic may be produced in a group of people with very different past histories, provided there is sufficient underlying anxiety in the group

The problems associated with repressed emotion are the problems of

human unhappiness, bereavement, insecurity and despair. For many of these civilization has as yet no adequate answer. Not infrequently, however, that aspect of the problem which affects the patient's health, may be improved by common sense advice, while just the opportunity to talk it out with another human being often throws a new light upon the issue and changes the patient's attitude towards it. This may be all that is necessary. Often the fact that the physician listens without censure to an account of the patient's mistakes and sorrows, does much to restore the patient's self-respect and gives him the needed courage to make his own decisions.

In the more serious emotional problems and personality disorders, the physician should turn to a neuropsychiatrist, but much may be accomplished by the general practitioner and by the specialists in other fields, once the problem has been revealed.

In closing I should like to emphasize two points: first, that organs and tissues which are the site of disease are not immune to the physiological and biochemical effects of emotional conflict, and second, that the most important conflicts in this respect are often those which the patient has forgotten.

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## THE ROLE OF THE NEW YORK ACADEMY OF MEDICINE IN THE DEVELOPMENT OF THE AMERICAN MUSEUM OF HEALTH\*

GEORGE BAEHR

THE New York Academy of Medicine and the medical profession of the City of New York have long had a deep and active interest in the establishment of a Museum of Medicine and Public Health in this city which might serve the City, the State and the Nation. Although many have recognized the need, special credit must be given to Dr D Bryson Delavan, a distinguished physician of this city, who persistently and ardently advocated its consideration over a long period of years. By 1927 his persistence had convinced Dr Linsly R Williams, then director of The New York Academy of Medicine, that the initiation of this project was one of the public responsibilities of the Academy.

In the year 1927, the Council of the Academy authorized the President of the Academy to appoint a special committee for the purpose of studying and stimulating the establishment of such a museum. The first committee appointed in 1928 included Dr Williams, Dr B Sachs, Dr John A Hartwell and Dr E H L Corwin. In 1933 a larger special committee on museum was created of which I have had the privilege of serving as chairman. It was hoped that the gradual accumulation of material for the proposed museum might ultimately result in encouraging the interest and the financial support of philanthropic foundations, of people of means and of the municipality. In the absence of more adequate storage and exhibition space in the Academy building it was decided to restrict the collection at first to material having a bearing upon the history and development of medicine. The main purpose, however, was not neglected, namely, to interest both governmental and private support for a museum of medicine and public health to serve the medical profession and the public. With this idea in mind, a conference was held at the Academy in 1931 between the Academy's Committee on Public Health

\* Address delivered at the dedication of the Medical and Public Health Building of the World's Fair, New York, June 17, 1939.

Relations and representatives of the American Public Health Association in the hope that these two organizations might collaborate, and when Rockefeller Center was under construction there was some hope for a time that space might be provided

At that time we had in mind a museum which would combine the best elements of the popular Hygienic Museum of Dresden with which I had been impressed in 1912 and the more scientific Wellcome Museum of London. It was our belief that, like New York's Museum of Natural History, a popular museum for health education must have the best professional leadership and a substantial scientific working background so that it might maintain the highest standards of scientific accuracy and progress and not degenerate into mere cheap and unmeritorious showmanship.

Five years ago, shortly after the inauguration of Mr. LaGuardia as Mayor of the City of New York, I had an opportunity to bring this subject to his attention. With his usual quickness of perception, he immediately grasped the significance to health education of a great museum, like our Museum of Natural History but devoted to problems of health and disease. Sometime in 1935, I was again called to see him. He told me in confidence of the news which had not yet been made public, that a World's Fair in New York City was under consideration. He reminded me of our previous conversation concerning a museum of medicine and public health and asked me to prepare a short brief on the subject which he might advance as one of the worthy reasons for holding a World's Fair in New York. It was his idea that a great non-commercial exhibit on medicine and public health should be created in such a manner and so comprehensively that it might serve as the nucleus for the future permanent museum which I had proposed to him. In this way, he suggested, our hopes might come to realization at the termination of the Fair in 1940, far sooner than we had dared to hope.

I then consulted with the officers of the Academy of Medicine and with Dr. Louis I. Dublin, recently president of the American Public Health Association. At his instigation, Dr. Victor Heiser and Mr. Homer Culver of the American Public Health Association met with me and assisted in preparing the brief. This brief and the continued interest of Mayor LaGuardia and Mr. George McAneny resulted in the appointment of the small working committee which developed this great project, the Medical and Public Health Building of New York's World Fair,



which we dedicate today, with the self sacrificing assistance of several hundred experts in all branches of medicine and public health. The composition of this small executive committee indicates how successful has been the collaboration of the three major participating interests, the City of New York, the medical profession and the field of public health. The interest of the City is represented on the committee by the Commissioners of Health and of Hospitals, the public health association by three representatives, the medical profession by four representatives, among whom I have had the privilege of representing The New York Academy of Medicine. The board of directors of the permanent American Museum of Health is now composed in a similar fashion, except that it includes distinguished citizens in addition to the city government and the major local and national organizations representing public health and medicine.

I speak not only on behalf of The New York Academy of Medicine, but also for the entire medical profession of the City of New York and for its five medical schools in assuring you of our continued devotion to this great enterprise. We fervently believe that it will be the center from which will emanate the developing techniques of health education for the people of our City and the Nation. To this center will come hundreds of physicians and public health officers for training in the modern methods of health education, and it will share its accumulating store of rich experience and its wealth of technical material with all the health and welfare agencies of the land.

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### DEATHS OF FELLOWS

COHN, FELIX 945 West End Avenue, New York City, born in Vienna, Austria, June 24, 1860, died in New York City, June 2, 1939, received the degree of Bachelor of Arts from the College of the City of New York in 1879, graduated in medicine from

the University of Heidelberg, Germany, in 1884, elected a Fellow of the Academy April 3, 1890

Dr Cohn had been consulting laryngologist and otologist to the Montefiore Hospital since 1912, the Lenox Hill Hospital since 1925 and the Beth Israel Hospital since 1930. He was a Fellow of the American Medical Association, a member of the American Academy of Ophthalmology and Otolaryngology, and the County and State Medical Societies.

Dr Cohn was the author of numerous publications on the ear, nose and throat.

## TWELFTH GRADUATE FORTNIGHT

OCTOBER 23 TO NOVEMBER 3, 1939

### *Arrangement of Afternoon Hospital Clinics*

Monday	October	23	Babies and Bellevue
Tuesday	October	24	Memorial and New York
Wednesday	October	25	Montefiore and Post-Graduate
Thursday	October	26	Mount Sinai and New York
Friday	October	27	Lenox Hill and Mount Sinai
Monday	October	30	Bellevue and Presbyterian-Neurological Institute
Tuesday	October	31	Montefiore and St. Luke's
Wednesday	November	1	Joint Diseases and Lenox Hill
Thursday	November	2	Morrisania and Post-Graduate
Friday	November	3	Sloane and Woman's

BULLETIN OF THE NEW YORK  
ACADEMY OF MEDICINE

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1939

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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



SEPTEMBER 1939

SOME DIFFICULTIES IN THE USE OF THE  
INSULINS IN DIABETIC PRACTICE\*

WALTER R. CAMPBELL

I<sup>N</sup> DISCUSSING the use of the insulins with an audience of practising physicians, it would seem advisable to confine attention largely to the products commercially available at present. Only two products, *Insulin* and *Protamine Zinc Insulin*, are licensed by the University of Toronto and accepted by the Council on Pharmacy and Chemistry of the American Medical Association at the present time. However, several other varieties of greater or less merit exist which may in the future supplant these.

Difficulties in the use of protamine zinc insulin arise in large measure from the fact that its properties have not been completely mastered, as well as from the fact that many physicians have failed to distinguish protamine insulin, which is still used in considerable amounts in Europe and was used in this part of the world in an experimental way for a short time, from the later product, protamine zinc insulin.

Numerous protamines exist and their combinations with insulin yield products with specific properties. Hagedorn first found that insulin

\*Read February 10, 1939 at The New York Academy of Medicine in the Friday Afternoon Lecture Series.

From the Department of Medicine, University of Toronto, and the Medical Service, Toronto General Hospital.

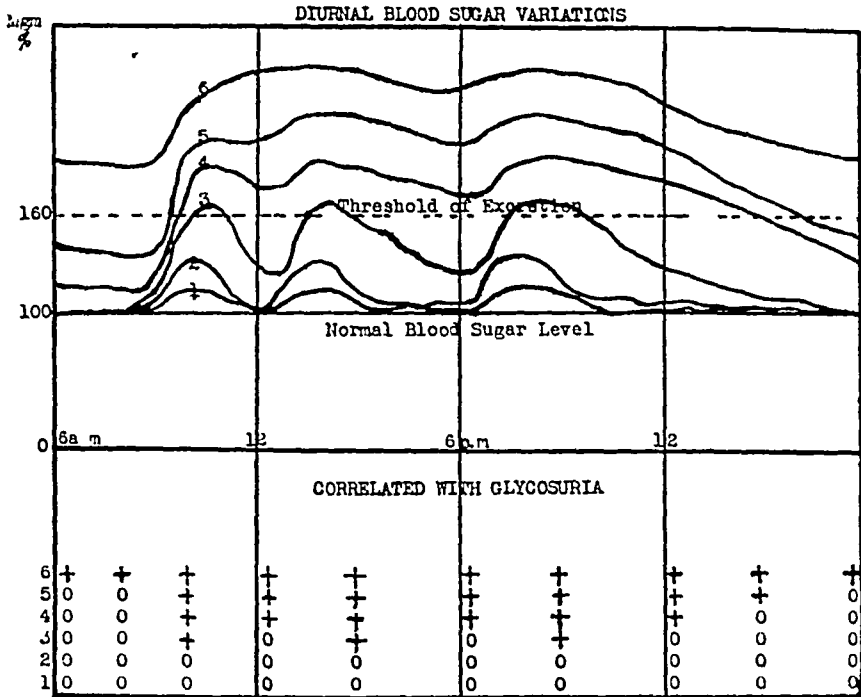


Chart I

combined with the protamine of the rainbow trout (*Salmo iridius*) had very desirable properties, a fact which was early confirmed by Joslin, Wilder and ourselves. But even more useful in certain respects was the insulin compound with king salmon protamine with which most of the experimental work on protamine insulin was carried out in America.

The investigations of Scott of the Connaught Laboratories, University of Toronto, showed a prolongation of action of insulin in animals by the addition of zinc and this we were likewise able to confirm in man, but the use of this product is accompanied by certain drawbacks. It became of great interest though to see whether or not the use of additional zinc might alter the properties of protamine insulin. Several new and very desirable properties were found to be possessed by this combination and it was made available commercially, under the name of protamine zinc insulin, as soon as adequate tests convinced us of its great value.

The first chart shows in a rather diagrammatic fashion the behavior of the blood sugar in normals and diabetics on an ordinary diet. In the normal individual there is a marked tendency to maintain the blood sugar level within certain definite limits. Nevertheless, following the

ingestion of meals, the blood sugar tends to rise somewhat for a short period and then to revert to a lower level within the normal band. Curves 1 and 2 are supposed to illustrate the fact that this is a variable phenomenon in different people. Seldom does the postprandial rise in normal individuals pass beyond 145 per cent. During the remainder of the twenty-four hours the blood sugar lies within the normal band. In other words, the normal variations in blood sugar do not pass beyond the level of the threshold of excretion, usually 160 per cent or a little higher, and no glycosuria results, as is indicated below. Glycosuria would result, however, if this threshold were lowered, producing the so-called renal glycosuria, and the greater the lowering of this threshold the more constant the glycosuria becomes. Occasionally this glycosuria cannot be stopped except by forcing the blood sugar to excessively low levels but, of course, this is never done as a practical measure of control. Renal glycosuria is a benign condition, an anomaly, requiring recognition rather than treatment. In Curve No. 3 we find the blood sugar starting within the normal values and rising after meals to overstep the threshold of excretion, glycosuria resulting at these times but disappearing as the blood sugar falls back to normal levels. This patient furnishes us with many problems. Numerous causes may produce this result: alimentary hyperglycemia, obesity, infection, liver disease, a lag type curve. But sometimes the patient is the mildest type of diabetic and peculiarly important because at this stage early strict treatment may wholly arrest the progress of the condition while he still has a high tolerance for carbohydrate or, perhaps, even bring about a cure. Curve 4 also starts within normal blood sugar limits but it rises above the threshold after a meal and continues thus, perhaps falling slightly before the next meal but rising again soon after this has been taken. After absorption of the evening meal the blood sugar falls to normal and remains so during the night. This patient is a mild diabetic, probably readily controllable by dietetic measures, but he introduces the question as to how much value he might gain from a period of support by a small supplement of a long acting insulin. Curve 5. Well marked fasting hyperglycemia with an increase above the threshold level after meals and long continued glycosuria, only ceasing during the night, is a stage of greater severity of diabetes, sometimes controllable by rigid dietary restrictions, and often benefited by small doses of insulin. In Curve 6 we have depicted the blood sugar level continuously above the



threshold level and constant glycosuria—a definite diabetic who will almost certainly require insulin to assist in metabolizing a suitable diet

In connection with Chart I there are several points to be noted a diabetic is not always continuously glycosuric, diabetes is not the most frequent cause of glycosuria, literally hundreds of other causes may operate but diabetes is the most constant and the most persistently recurrent cause of hyperglycemia and glycosuria as well as the probable cause of maximal deviations from normal values Diabetes varies in severity Besides other features which may often assist in diagnosis, both hyperglycemia and glycosuria either constant or persistently recurrent, are necessary for the diagnosis in most cases

Chart II All diabetics do not need insulin When placed on restricted diet the mild diabetic promptly becomes sugar free Some patients, however, become aglycosuric with greater difficulty and only after some days Perhaps they may require insulin to assist in metabolizing more liberal diets required for their daily work A third group will not become sugar free, and insulin definitely is necessary for these patients A test period on restricted diet would eliminate many of those cases now placed unnecessarily on insulin and later found not to require it I am not unmindful of the fact that in certain instances insulin administered to mild and early cases may sometimes be of value in ameliorating their severity, but on this subject too little data now exist Their recognition is largely dependent upon adequate preliminary testing of their tolerance In such a group with high initial tolerance there will be few difficulties to overcome in connection with the administration of insulin One recognizes the greater stability of the normal individual to a given dose of insulin, these mild diabetics resemble normal individuals in this respect more than the severe cases of diabetes mellitus

Reference to our early work on insulin will indicate that such insulins did possess a more prolonged action than the regular type now available commercially Through the years, as purity of the product was increased, the action became more explosive, as it were, and an increasing number of doses was required to manage severe cases of diabetes Whether the original long action was due to their high zinc content, which Scott has shown definitely prolongs the action of insulin, or to other adjuvants now refined out of the product, is not now known, but one may contrast the twenty-four hour action of early insulin, as shown in Chart III Curve 1, with the more rapid action of

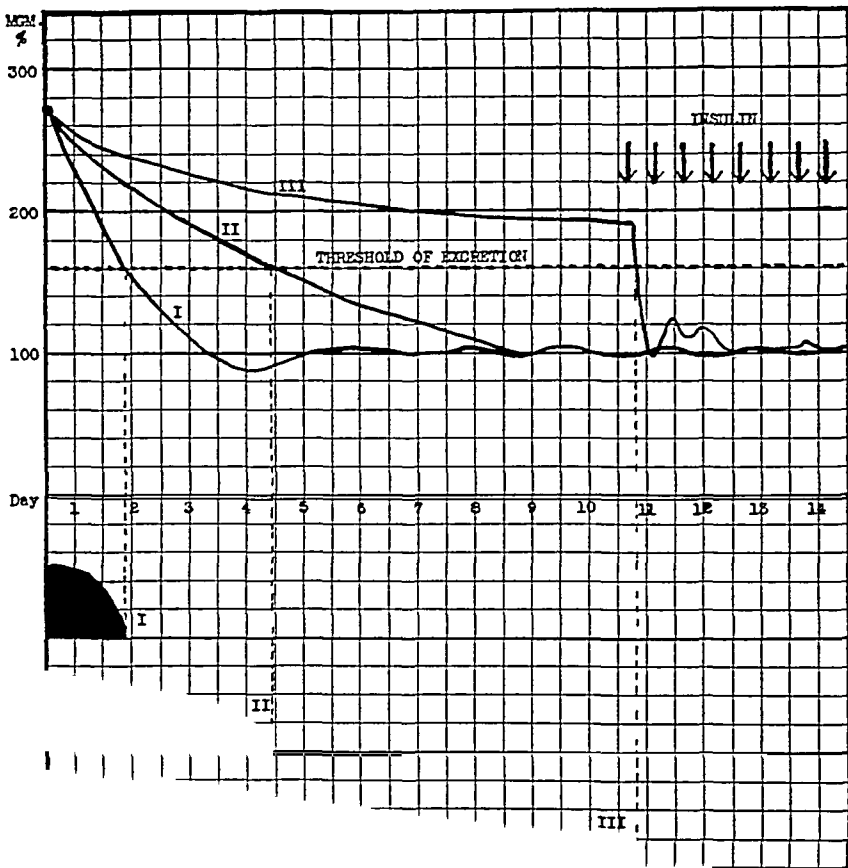


Chart II—Hyperglycemia and glycosuria in I, mild, II, moderately severe, and III, severe diabetics under treatment

1936 insulin in Curve 2. In the latter, the action is wholly completed before the older preparations had caused their maximum fall of blood sugar.

The third curve on Chart III shows the effect of an equal dose of Hagedorn's salmaridin protamine insulin in the same individuals. As will be noted, the action is more gentle and more prolonged than that of the unmodified preparation. Without doubt the modification of insulin by means of protamine and other substances has made possible the greatest improvement in diabetic treatment since the introduction of insulin itself.

How, then, does protamine zinc insulin differ from ordinary or unmodified insulin? I have endeavored to answer this in part in Chart

## 1922 INSULIN

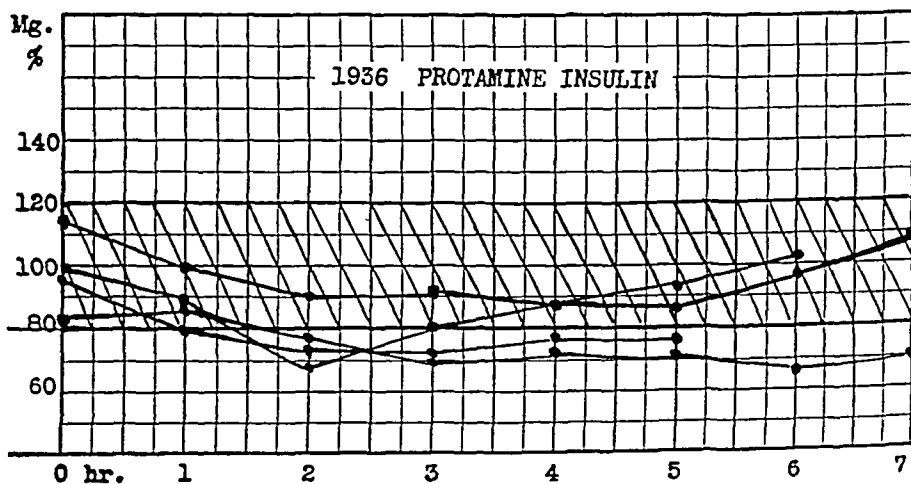
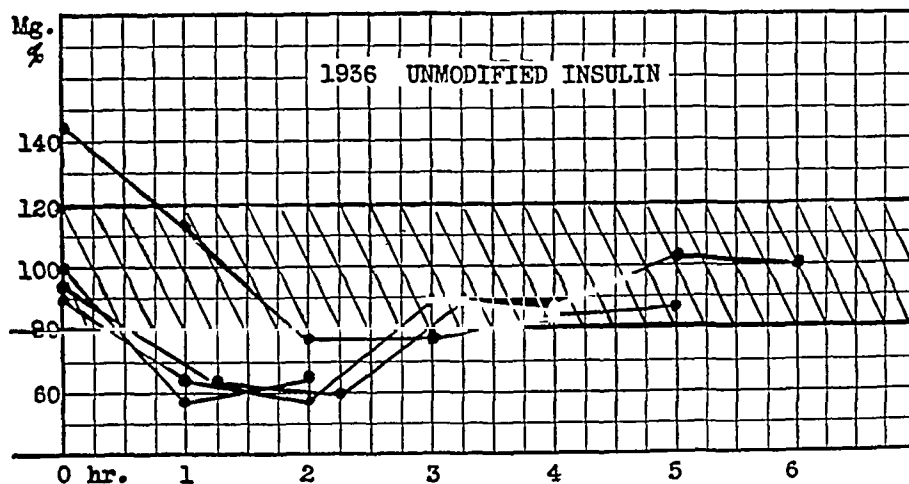
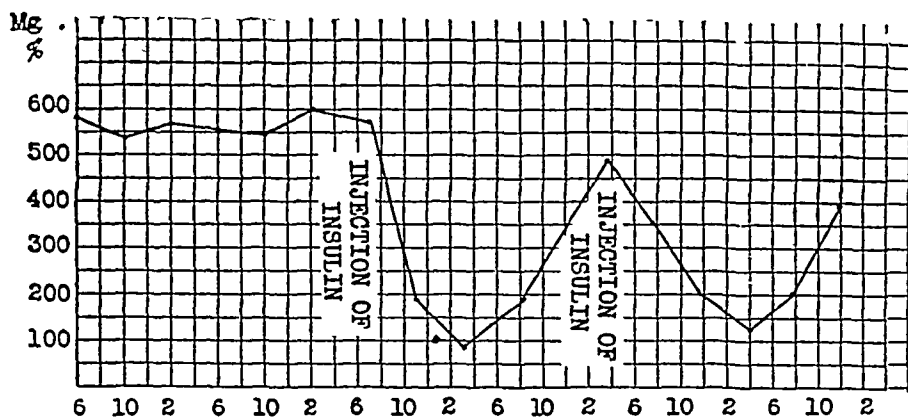


Chart III

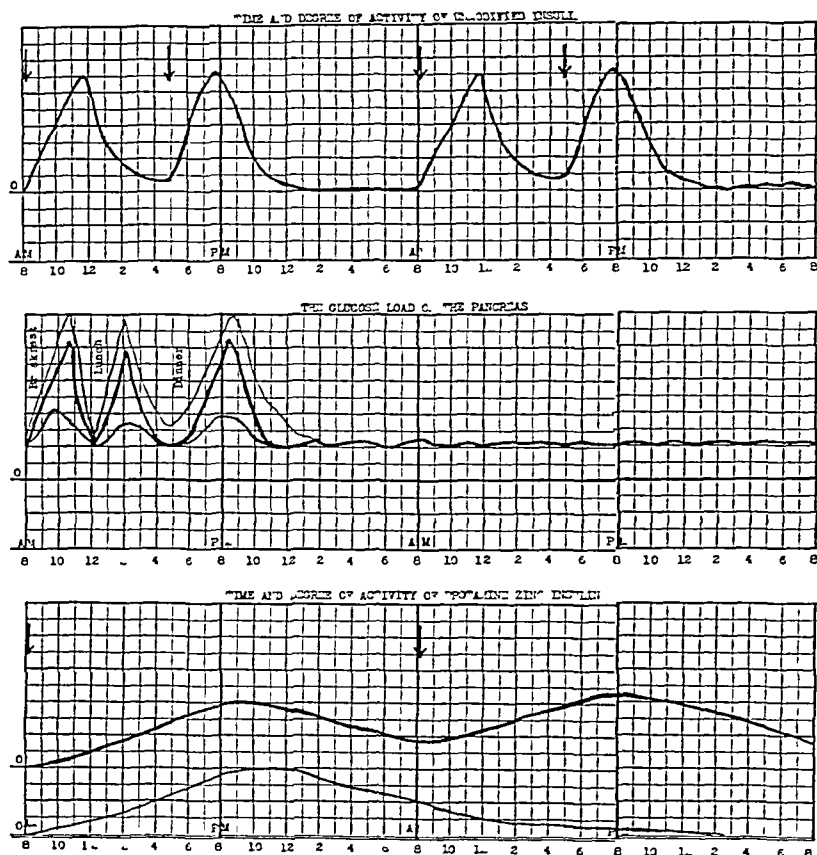


Chart IV

IV Regular insulin is a solution and when injected is rapidly absorbed and available early to do its work but, as you will have noted previously, its action is now of short duration. If we allow the squares of Curve 1 to represent some hypothetical unit of efficiency, then the curve of insulin activity outlines the amount of work performed and we see that the diabetic given two doses of such an insulin in a day gets rapid large effect which is completed early, and during the night hours the patient is left dependent upon such insulin as he can produce himself. Quite probably, if the carbohydrate intake is not excessive, the pancreas supplies but little insulin during the period of action of the injected insulin and a greater amount of the patient's own insulin is available for the night hours. It is also true that during fasting or during the night a comparatively small amount of insulin is required but the relatively small store of glycogen soon is used up. The patient falls back on

protein utilization to obtain the necessary energy to live and by morning the blood sugar of the patient rises to abnormal levels unless suitable further injections are introduced or unless the patient has sufficient insulin production of his own to counteract this process. In other words, in the case of patients with small insulin production or patients on high calory or high carbohydrate diets with unmodified insulin, the diabetic tendency is mastered for only a few hours of the day, the remainder of the time he is only a little less diabetic than before. Particularly is this true of patients who are allowed to have high blood sugar or a little glycosuria as often has been done, allegedly to protect them from the dangers of nocturnal reactions.

Before contrasting these effects with those of protamine zinc insulin, we may examine Curve 2, which represents what I conceive to be the normal distribution of the glucose load on the pancreas, meaning by this not only the absorbed carbohydrate as such but also that derived from the glycerine of fat and the breaking down of protein. The starting point of the curve, being somewhat above the zero line, is intended to represent the fact that some insulin is required normally for endogenous metabolism even during fasting. However, immediately the carbohydrates from the meals commence to be absorbed, this load is increased in degrees varying with the amount absorbed. Following the absorption of food the load falls to a lower level which persists throughout the night. Now, comparing this curve with Curve 1, we see that regular insulin is most usefully employed to counteract the effect of the ingested carbohydrate. The more effectively these two factors are balanced, the better the patient's own insulin can be used to maintain a normal state during the night. In many cases this has been found to be actually insufficient and small supplementary doses are required to keep the patient normal during this period. It is apparent, then, that a longer acting insulin would be desirable to reduce the number of doses of insulin required and to maintain the normal metabolism of the patient for a longer period of time.

Salmaridin protamine insulin provided a partial answer to these requirements, being effective in maintaining normal metabolism for some sixteen hours. Onchorhynchin protamine insulin was effective for some twenty-two hours. Chart III indicates that the zinc modification of onchorhynchin protamine insulin has a still longer effect. Taking the lower line, the curve indicates that, though the slow absorption of the

suspension of this product makes a high degree of activity impossible, the activity is continued in useful amounts for some thirty hours. Indeed, Wilder has shown that some activity is present for fifty-seven hours, similarly my colleague, Dr Fletcher, has obtained evidence that a minimal degree of activity persists for some sixty hours during partial fasting. The upper curve represents the fact that the effect of successive daily doses of protamine zinc insulin is cumulative to some degree. Yesterday morning's insulin helps to provide in part for the metabolism of today's breakfast.

Comparing the action of this insulin with the glucose load on the pancreas, Curve 2 indicates that it will be most effective in balancing the constant load of the endogenous metabolism on the insulin-producing mechanism rather than in ironing out the peaks in the curve induced by the absorption of food. *The maximal useful dose of protamine zinc insulin is that which leaves the patient with a low normal fasting blood sugar without nocturnal hypoglycemia.* By this means he attains the largest margin between the fasting blood sugar level and the threshold of excretion after breakfast, and somewhat better rest for the pancreas during the night so that any self-manufactured insulin may be devoted to controlling the absorptive hyperglycemia. Possibly this rest accounts also for the slow reduction in insulin requirement noted in so many cases. As the new injection of insulin is gradually absorbed and reaches its maximum level, larger amounts of carbohydrates may be placed in the later meals of the day. However, protamine zinc insulin alone is ill adapted to the consumption of high carbohydrate diet and any hyperglycemia or glycosuria encountered is very slowly controlled. One may attempt to counteract this, as well as the tendency to nocturnal hypoglycemia because of overdosage of insulin, by putting a portion of the carbohydrates into a bedtime lunch, but this procedure is not entirely satisfactory. Prolonging the digestive and absorptive period by suitable selection of food may lower the peak of the load and permit the use of 5 to 8 units of more long-acting insulin. This may be done in suitable cases by using unripe bananas, by smothering berries or peaches with cream, by using heavy cream or butter on oatmeal or puffed cereals, by using fat meats, French-fried potatoes and French sticks or Vienna rolls liberally spread with butter. With long-acting insulin the problem of evening refreshments can be solved safely by taking a supper somewhat lower in carbohydrate than usual and selecting suitable refresh-

ments One of my patients, whose severe diabetes remains unknown to his associates for business reasons, has made himself popular with hostesses by his activities in serving the evening refreshments No one ever notices that he has no time to eat more than a small sandwich, a few nuts, or drink a cup of coffee If it appears necessary to take more, he walks home "to clear his head of the smoke" The walk uses up a little more carbohydrate He has never had glycosuria or hypoglycemia since going on protamine zinc insulin nearly three years ago

It must be clear that protamine zinc insulin has but a limited capacity to take care of ingested carbohydrate and that treatment is more successful with the lower carbohydrate diets than with those containing a more liberal amount Roughly, it may be said that severe diabetics cannot take a diet exceeding 100 grams of carbohydrate (or 150 grams total glucose) while using a single morning dose of protamine zinc insulin An attempt to do so results in glycosuria, hypoglycemia or both With diabetes of lesser severity a larger amount of carbohydrate can be utilized by giving the protamine zinc insulin in amounts sufficient to produce a low normal fasting blood sugar without hypoglycemia and utilizing the remaining pancreatic efficiency to counteract the postprandial hyperglycemia and glycosuria Successful treatment, according to my criteria—adequate caloric intake and maintenance of the blood sugar within normal limits—becomes more and more difficult to attain as the carbohydrate in the diet rises, but sometimes is accomplished if the total calories can be kept low Amounts of carbohydrate much above 150 grams, in my opinion, are usually unwise unless it is necessary to provide more because of failure of lipase secretion by the pancreas Many patients on diets containing 250 grams of carbohydrate would be better on a lower carbohydrate ration without insulin

In the fasting state the slowly absorbed insulin is definitely more economical than regular insulin Fewer units are required and in addition hypoglycemia is not so much to be feared If calories are allowed at a working level, this economy diminishes as carbohydrate in the diet increases When the carbohydrate of the diet is below 100 grams, 60 per cent as much protamine zinc insulin as regular insulin will be equally effective At 100 to 125 grams of carbohydrate, 75 per cent as much protamine zinc insulin as regular insulin will be required But little economy is observed when more than 150 grams of carbohydrate are given in a working diet On the other hand, if undernutrition diets are

prescribed, considerable economy is observed with somewhat larger carbohydrate allowances

To many, the plan of giving protamine zinc insulin in small and gradually increasing doses from the beginning of treatment commends itself, especially if ambulatory treatment is necessary. There are numerous advantages in commencing treatment under hospital conditions, however. In this case it seems preferable to determine whether the patient can metabolize a basal diet and then increase the food allowance in ladder fashion towards the maintenance level, using regular insulin, if necessary, as the required period of observation is far shorter than if protamine zinc insulin is used. In transferring patients from regular insulin to protamine zinc insulin, doses up to 75 units per day of the unmodified insulin are substituted by 60 per cent as much protamine zinc insulin given in a single morning dose. However, since the insulin from this injection is absorbed slowly, it is probable that glycosuria may occur prior to the insulin becoming available. To obviate this, 60 per cent of the balance of the original dose of regular insulin is given with the first dose of protamine zinc insulin and the remainder of the regular insulin before the evening meal. On the following day, the morning dose of protamine zinc insulin is accompanied again by regular insulin, as before, but thereafter it is discontinued.

If a patient attains a low normal fasting blood sugar level without nocturnal hypoglycemia on a given dietary regime, but shows glycosuria, examination of urine collected every two hours is indicated to determine the time of the glycosuria. Onset of glycosuria, not duration, is the more important, though large increases in glycosuria following the later meals are also significant. Not infrequently some rearrangement of amounts of carbohydrate in the various meals may cause the glycosuria to disappear. Spreading the meals over a larger number of hours or smothering the carbohydrate in fat, as suggested by Pollack, may be tried, or even a bedtime lunch which may make possible a few more units of insulin without inducing hypoglycemia. Should these measures fail, one is faced with the alternative of using less carbohydrate in the diet or of reinforcing the action of the protamine zinc insulin and of the pancreas with some regular insulin. With severe diabetics reinforcing with regular insulin nearly always will be required, as also is usually the case when very high carbohydrate allowances are made without shrinking the total calories. Regular insulin should be adminis-



tered in addition to the previous dose of protamine zinc insulin at first, though later it is probable that the protamine zinc insulin may be reduced somewhat. Preferably, regular insulin should be given in the morning, close to breakfast time, and it is most convenient to give the protamine zinc insulin at the same time. With protamine zinc insulin, as opposed to the more rapidly acting protamine insulin, there is comparatively little to be gained by shifting the time of injection by one or two hours, so that giving it with the breakfast does not matter except as a minor inconvenience to the patient.

Attention should be called to a detail which sometimes is neglected. Adjustment of the insulins to the requirement of the resting individual is frequently not the most satisfactory for the working individual. The perfectly adjusted hospital patient frequently has difficulty with hypoglycemia on his return to working conditions. I feel that there is little doubt that gradual increases in the diet to a working level give the most satisfactory results in treating the diabetic but, in approaching the working level of the diet from below, it is desirable to arrange increases in activity, such as walks or occupational therapy, to simulate the working conditions of the patient and thus avoid abrupt alteration of conditions on discharge from hospital. A little more attention to this point would avoid many of the difficulties and disappointments now being experienced with protamine zinc insulin.

An occasional cause of glycosuria and, later, hypoglycemia may be the failure of the patient to observe the caution to mix thoroughly the suspension of protamine zinc insulin in the bottle before removing the dose. Neither insulin should ever be injected intramuscularly because of the injury to muscle tissue, and protamine zinc insulin should not be injected intravenously as most of the prolonged effect is lost and the patient is subjected to a certain amount of danger from the protamine itself.

It may not be amiss to point out here that when we were working with protamine insulin I introduced the method of layering the two insulins in the same syringe and injecting them through one skin puncture in two places under the skin. This was a convenience but is not possible with protamine zinc insulin. For stabilization purposes, protamine zinc insulin contains both excess protamine and excess zinc so that, if mixed in the tissues, all will become protamine zinc insulin. However, it is still possible to avoid the pain of a second skin puncture.

by using three-quarter inch needles and two syringes. A needle is attached to the syringe containing regular insulin, plunged far, but not deeply, under the skin and the contents injected, the needle is almost withdrawn, its direction changed, and again inserted to a point some distance from the original injection, the empty syringe is now removed, a syringe containing protamine zinc insulin substituted and its contents injected.

The more severe the diabetes, and the higher the carbohydrate content of the diet, the more likelihood there is that more than one daily dose of insulin will be required. In my experience, when more than 50 units of protamine zinc insulin are required, it is comparatively seldom that the long acting insulin alone will adequately control the patient's metabolism. In such instances the change-over morning dose of regular insulin, mentioned above, may be continued and usually it will be found advisable within the next few days to reduce the protamine zinc insulin to 50 per cent of the amount of regular insulin originally used. No absolute rule can be laid down, however, since results are so much dependent upon the original tolerance of the individual, the total calories and the proportion of the diet made up of carbohydrate substances. The useful dose of protamine zinc insulin is limited by the production of nocturnal hypoglycemia. This must be avoided. At the same time, it is desirable to use sufficient protamine zinc insulin to ensure a low normal fasting blood sugar in the morning. From this basis the appropriate amount of regular insulin may be worked out by watching the post-prandial hyperglycemia and glycosuria. Experiments have been made giving the protamine zinc insulin at various times of the day, and sometimes these are successful. Administration of protamine zinc insulin at eleven o'clock at night, so that its maximal action occurs around breakfast time in the morning, occasionally has some advantages. However, it frequently results in hypoglycemia before breakfast. Administration of two smaller doses, morning and evening, may result in utilization of more carbohydrate although it does away with the convenience of a single injection. With some few patients it may be necessary to give protamine zinc insulin in the morning together with regular insulin, and to administer a second dose of regular insulin later in the day in order to keep the patient free of glycosuria. In these cases I have noticed that this usually is a temporary requirement and that later presumably because of the benefits of rest to the pancreas the evening dose can be

may be reinforced by regular insulin at any time, if necessary. Protamine zinc insulin will do the work if time is available. However, it is not always wise to allay the alarm of the careless patient and his neglectful relatives.

Coma is an emergency and should be treated as such. Today patients die, not of coma, but of the circulatory failure induced by coma. Properly treated with large doses of regular insulin, they should be out of coma before any considerable effect could be expected from protamine zinc insulin. To smooth the course of the immediate after-treatment and to prevent protein breakdown between periods of activity of the regular insulin, a dose of protamine zinc insulin administered early might serve a useful purpose. But if sufficient regular insulin is being used to ensure maximal conversion of metabolism to a carbohydrate type, it is difficult to imagine any occasion for its employment.

When Fletcher and I first described the clinical syndrome hypoglycemia, we felt it of the utmost importance to impress on those using insulin the dangers of the new drug. Insulin hypoglycemia is still dangerous but, in most instances, not to the degree we had anticipated. Today, insulin hypoglycemia, when induced by protamine zinc insulin, is dangerous in comparison with regular insulin, but the number of reactions is cut down materially. The danger lies partly in the insidious onset of hypoglycemia and in the tendency to recur when once cured with soluble carbohydrate. The older symptoms were associated with speed in the fall of the blood sugar, the newer insulin often steals away the blood sugar so gradually as to excite almost no symptoms until severe reaction levels are attained. Also, even with the immediate reaction cured, the remaining unabsorbed insulin on entering the blood stream may cause repetition of the reaction some hours later. While the well-known symptoms are encountered in some cases, hypoglycemia with the new insulin is often accompanied by a sensation of undue fatigue, negativism, slight headache or nausea and evidences that the normal repressions are lacking. Signs of deficient cerebral control, as in mild alcoholic intoxication, are more prominent features of the new picture. Somewhat greater difficulty is experienced in controlling reactions which have progressed to this blood sugar level but soluble carbohydrate administered by mouth is effective usually and can be reinforced by intravenous glucose if necessary. Until some starchy food is obtainable, soluble carbohydrate in small doses should be repeated each thirty

minutes Bread and honey or bread and corn syrup form an effective antidote both for the immediate relief of the patient and for his protection against a subsequent attack when more insulin has been absorbed into the blood stream from the site of injection

Unless precipitated by gross overdosage, fasting, indigestion, diarrhea or unusual and excessive exercise, reactions due to protamine zinc insulin administered in the morning will occur after six o'clock in the evening With protamine zinc insulin, a reaction due to exercise may be delayed for many hours Therefore, marked variations in the routine of living from one day to another should be avoided as much as possible to minimize this risk When both insulins are being used in the morning, any reaction due to regular insulin will occur during the day and if a supplementary dose of regular insulin is used at supper time, a reaction due to it will occur before midnight While not invariable, these rules indicate which insulin may require reduction Not less than five units should be removed from a protamine insulin dose while two units reduction may suffice to abolish hypoglycemia from the regular insulin

Local swelling due to the injection of protamine zinc insulin continues longer than that from unmodified insulin and may cause more prolonged discomfort Sensitization reactions sometimes appear with increased local swelling edema, urticaria, pruritus and even general symptoms may occur on rare occasions In my own experience these have been usually of minor importance and were allayed by cold compresses or by allowing a saturated solution of magnesium sulphate to dry on the skin Spontaneous desensitization usually will occur in two to three weeks if treatment is continued More severe degrees of sensitization occur in patients who are already sensitive to the protein of the species from which the insulin is derived or in patients who have discontinued the use of insulin at some previous time These are due usually to sensitization to the accompanying traces of species' protein but occasionally are due to insulin itself When due to protein sensitization, another preparation of protamine zinc insulin may be tried or the patient may be given regular insulin derived from another species for a time, then gradually desensitized by substitution of small, but gradually increasing, doses of the offending insulin Alternatively, crystallized insulin may be used and gradual desensitization carried out If the patient is sensitive to insulin itself, he may be placed on an under-nutrition diet and desensitization carried out with crystallized insulin either by the

Besredka or by the slow method, injecting the insulin in approximately the same spot repeatedly, as local desensitization precedes the general process

Though antigenic properties of protamines have been denied, some cases of sensitization have been stated to occur. It is far from clear that they are not due to slight traces of accompanying fish protein rather than to the protamine itself. We have failed thus far to encounter this difficulty which doubtless could be surmounted by placing the patient on unmodified insulin temporarily and desensitizing with small doses of protamine zinc insulin or pure protamine solutions.

The greatest source of difficulty with protamine zinc insulin is impatience. This insulin is slow acting and cumulative and time is required for its full action to develop. Premature increase in the dose to hasten the action results in hypoglycemia, though on the same day the patient may have had glycosuria from the carbohydrate of the meals. Not less than four to seven days on a certain regimen is adequate to determine whether it is satisfactory, though it may be possible in shorter time to determine that a program is unsatisfactory. Hasty conclusions on this point should be avoided.

Finally, with adequate preliminary investigation and control, all diabetic patients requiring insulin will do better on protamine zinc insulin, or on a combination of protamine zinc insulin and regular insulin. No suggestion that a complete solution of the problems of the most severe and unstable cases of diabetes has been accomplished is warranted but we have been gratified to find that better control of such cases may be obtained by the use of protamine zinc insulin than was previously possible and many are markedly improved. For those with a lesser degree of severity, one may say there is an improvement in their general health, a reduction of the number of doses, economy of insulin, improvement of the twenty-four hour blood sugar level, and superior control of azoturia and ketonemia. There is also a diminution in the frequency of reactions though, when these do occur, they may be more difficult to diagnose and treat effectively. The patient has much greater freedom of action, and there are numerous indications that a slow but very definite improvement of tolerance occurs in some cases. Protamine zinc insulin has multiplied the problems of the physician treating the patient but for the latter, when he has been successfully stabilized, the outlook is improved immeasurably.

## THE TREATMENT OF POSTABORTAL AND POSTPARTUM SEPSIS, WITH SPECIAL CONSIDERATION OF SULFANILAMIDE AND ALLIED DRUGS\*

EDWARD G. WATERS

I **N** CONSIDERING new therapy for old diseases, we must not repeat an error of the eighteenth century, when the medical world forgot the teachings of White of Manchester, grudgingly to relearn them seventy years later from Semmelweis. There is much new to be learned and much old to be remembered in the treatment of postabortal and postpartum sepsis.

Postabortal sepsis usually follows induced, rarely spontaneous, abortions. There is generally the element of reinvasion of the uterine cavity without adequate asepsis, and usually there is retained detritus. Since the uterus is of smaller size than in the postpartum state, with less developed venous circulation, septic thrombophlebitis is less often seen than in puerperal sepsis, and subinvolution is not a common factor in causing postabortal bleeding. Traumatic invasion of the uterine wall or perforation make direct peritonitis a more common complication in postabortal infections. Therapy in postabortal sepsis more frequently demands gentle removal of infected, necrotic intrauterine debris, than in postpartum infections. Otherwise, these two conditions resulting from septic invasion of a uterus recently pregnant may be considered together from the standpoint of therapy.

Before detailing treatment, it is important first to consider some of the factors and agents which make it necessary. We have spoken of unclean intrauterine manipulation followed by reinvasion, with incomplete emptying of the uterine contents, as responsible for an overwhelming majority of postabortal septic cases. Here as in postpartum sepsis, we have bacterial transplant into a fertile field with open tissue spaces and vessels. In postpartum sepsis there is generally a history of long, exhausting labor with terminal traumatizing operative vaginal delivery,

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associated with larger breaks in continuity of tissue than is commonly encountered with spontaneous vaginal delivery. But we must remember that even in normal cases, the uteroplacental site is a huge open wound, filled with soft blood clots occluding large sinuses, and the cervix is the site of multiple small abrasions and areas of superficial necrosis. Obviously, the groundwork for bacterial invasion is always present in the postpregnant genital tract.

Infective organisms must come from somewhere to produce infection and the sources are either endogenous, from the patient herself, or exogenous, introduced by another person, directly or indirectly. We cannot deny the possibility that the normal bacteria in the vagina suddenly change from innocuous to virulent forms when conditions are unusually favorable. But we do know that such change is unusual and that a bacterium generally maintains and seldom alters the inborn virulence of its own generation. A marked depression in the resistive factors of an individual might endow such an organism with a relative increase in virulence. This is true especially of the anaerobic non-hemolytic streptococcus. But it is my belief that most bacteria of high invasive properties are introduced shortly before, during or after the uterus is emptied. The high proportion of infected cases occurring in women who have had exhausting labors and traumatizing deliveries, pregnancy toxemias, chronic systemic disease, or excessive blood loss is significant. It suggests that invasion and diffusion, which characterize the degree of bacterial virulence, are also dependent upon lowered resistive factors.

An analysis of operative deliveries will show morbidity thrice that for normal cases if the membranes have been ruptured and/or the patient in labor more than twelve hours. Likewise, vaginal examinations introduce a danger that becomes serious when they are unclean or frequently done. Routine rectal examinations are far safer for the mother, and inherent hazards for the fetus are minimized by supplementing rectal with vaginal examinations when in doubt.

Certain changes in the maternal organism, such as increased blood volume, increased circulatory, metabolic and cellular activity, and increased phagocytosis, promote greater resistance to infection during pregnancy. Over and above this are the natural resistive factors to be found in all fixed and circulating tissues, and in the event of infection, acquired immunity developing in the host.

The types of organisms are numerous including various strains of streptococci hemolytic, non-hemolytic, aerobic and anaerobic, various staphylococci, colon bacillus, gonococcus and pneumococcus, as well as the gas-forming anaerobes. The streptococcus and staphylococcus account for about 95 per cent of all puerperal infection, and nine of ten cases assuming any serious degree of virulence are caused by streptococci. The gonococcus and colon bacillus rarely cause virulent sepsis, the latter is generally a parasite or saprophyte.

The pleomorphic character of the infecting agent, and the varying response of the host make the determination of the responsible organism almost indispensable to antibacterial therapy. But with streptococci and staphylococci accounting for nearly 95 per cent of all postabortal and postpartum sepsis, we may presume one of these to be the active agent when bacteriologically it is impossible to indict the responsible organism. This, as we shall see, is an important therapeutic premise.

#### MANNER OF INVASION

There are two routes by which invasion of the infecting organism progresses

- 1 Through the vessels at the placental site. This is often seen in virulent postpartum streptococcic infections or with infected incomplete abortions. Then, too, extension of this infection with thrombosis of the veins in the broad ligaments is commonly seen with organisms of low virulence, generally emanating from infected veins in the sub-placental area. Here most commonly noted are the anaerobic streptococci which pass on to low-grade pelvic thrombophlebitis. While there is much concerning thrombus formation which we do not know, one fact we do know is that the most important factor in the production of a thrombus is venous wall infection, whether it gets there by way of perivenous lymphatics or through the damaged endothelial lining. With infection at the uteroplacental site, the infecting organism reaches the lacerated vessels and initiates a process, the extent of which is determined by the character of the organism, the resistance of the host, and the rapidity with which the resistive forces can be mobilized. With a virulent organism and little resistance the thrombosis may not extend beyond the uterine wall and the patient may succumb within a few days with no involvement of the larger veins. With marked resistance and lessened virulence the process of thrombus formation may progressively in-



volve the vessels of the broad ligament, pelvis and the vena cava, and the duration of the infection may last for weeks. The frequent occurrence of emboli and infarction complicates the picture and alters the treatment.

2 Through the lymphatics. Infection by way of the lymphatics of the uterus and broad ligament, and reaching the general circulation through the thoracic duct, is another path of invasion. This route is not commonly followed but when occurring, is associated with a highly virulent form of general sepsis, with a paucity of pelvic symptoms and pathology. Peritonitis may occur subsequent to lymphatic invasion, through extension from the broad ligament or subserosal lymphatics to the peritoneum.

### PROPHYLAXIS

The lessening of the incidence of infection and death from abortions lies in respect for moral and medical ethics and in abolishing the performance of surgically unclean abortions. Where therapeutic abortion is indicated, proper hospital management and care will adequately solve the problem. Judicious distribution of adequate instruction in birth control should minimize the need for abortions.

Prophylaxis of puerperal infections can be summed up in two words—good obstetrics. We may subdivide those two words into their applicable component parts: 1) during pregnancy, 2) during labor, 3) during delivery and 4) in the postpartum state. Prenatally, it is necessary to appraise the general condition of every mother through complete physical examination with detection of any systemic disturbances or abnormalities. An adequate and proper pelvic examination will give an estimation of the pelvic capacity upon which a prognosis can be made before labor begins. Avoiding the development of toxemias is also imperative since they notably increase the incidence of puerperal sepsis. Proper dietary control with intake of vitamins A, C and D, especially in the last half of pregnancy, requires stressing. Oral cleanliness and routine gargling is advocated for all patients with a history of recurrent sore throat and upper respiratory infections. Common sense observation of the patient, in addition to the use of the stethoscope, the manometer, the test tube, and weight scale, afford protection to most expectant mothers.

During labor a few essentials must be observed. Any examination must be cleanly made, whether rectal or vaginal. Rectal examinations

in the presence of a vaginal discharge require care, since the posterior vaginal wall must be pressed against the cervix. No pregnant patient should be touched during labor by an attendant without thoroughly scrubbed hands. A mask, preferably an impermeable type of mask, should be used during an examination. The vulva of the patient must be properly prepared and cleansed. There is considerable difference of opinion as to the value of vaginal antiseptics routinely used during labor. Reports as to their value are contradictory, yet it would seem good sense to use some worthwhile type of intravaginal antiseptics in all patients who present themselves in labor with a vaginal discharge. All personal contacts with patients in labor should be checked and recorded, and streptococcus carriers, especially those with infections in the upper respiratory passages, should be barred from labor and delivery rooms. All potentially or actually infected patients should be isolated and treated apart from the others in labor.

*During Delivery* The infection rate is high in patients with long labors and ruptured membranes especially when complicated by traumatizing delivery. It is important to recognize early in the second stage the need for terminating labor by operation, if one would avoid an unduly high incidence of infection. Prolonged general anesthesia is to be condemned, for properly given spinal anesthesia, gas-oxygen, or local anesthesia with a patient well under analgesia, is far safer. During labor the patient should be protected against undue exposure and heat loss. Excessive loss of blood during delivery materially lessens resistance. The "12-hour safe period" should be observed for cesarean section cases. This means that the operator should decide, if able, within twelve hours of the onset of labor or within twelve hours of the rupture of the membranes as to whether or not a cesarean section need be done. The incidence of infection in this group under twelve hours is not higher than for vaginal deliveries. Where the membranes have long been ruptured and the patient long in labor, with or without fever, an extra-peritoneal cesarean section should be seriously considered. It will protect from marked morbidity, and possible death, many patients in the potentially infected groups.

*Postpartum* Excessive blood loss should be replaced by transfusion, with intravenous glucose to maintain blood volume and pressure until blood is available. Every bleeding and every toxic case should be typed before delivery and a suitable donor held within call. Involution should

be hastened by the use of oxytocics. Prophylactic chemotherapy, of which I shall presently speak, should be used in presumably infected cases. All symptoms of shock should be overcome immediately. In applying the postpartum perineal pads one should avoid massaging bowel content into the vagina. Extreme care is needed when catheterizing the patient and giving enemas, especially when perineal incisions or lacerations exist. The perineal attendant should be masked, and if there are any upper respiratory infections, nothing but an impervious mask should be used. All infected cases should be isolated.

### TREATMENT

Since the patient's recovery depends upon the outcome of a battle between the invading organism, with its virulence, volume and rapidity of spread unknown, and the patient's own resistive forces, obviously it is all important to assist in conserving her mental, moral and physical resources. She is kept happy in a light, airy room, free from noise and disturbance. An appetizing, high caloric diet supplements copious water and fruit-juice ingestion. High position in bed and frequent, gentle turnings combat hypostasis without involving too great danger from thrombotic emboli. A low enema daily evacuates the bowel, and distention is relieved by rectal tube and injections of prostigmin or pitressin. Relief of pain and avoidance of exhaustion call for pantopon or morphine, and denial of visitors. Diarrhea is checked with starch and opium enemas, and alcohol sponging with ice caps to the head symptomatically relieves the hyperpyretic crises. The only surgical treatment of post-abortal infections consists in removing retained infected detritus from the uterus with sponge stick and forceps. Cul de sac abscess and pus accumulations pointing in the inguinal region, occasionally seen in post-abortum or postpartum sepsis, require draining when pus is present in a recognizable amount. Unless the uterus must be emptied of its contents because of hemorrhage, it is usually best left alone. Douching is employed only to remove the fetid material and discharge which is commonly noted in anaerobic infections. Oxytocics and short wave therapy hasten involution. When in doubt the safest thing by far is non-manipulation of the uterus.

It is necessary to actively combat the invading bacteria. There are ways in which this may be attempted, namely, vaccine therapy, serum therapy, non-specific therapy, blood transfusion and chemotherapy.

Vaccine therapy has been largely abandoned in the treatment of puerperal and postabortal sepsis, and there is no reputable record indicating that it is of value. The time element alone militates against its success. Active immunization is of doubtful theoretic worth. Too many patients would have to be immunized against too many possible infections to make it seem worth the effort.

Serum therapy is not new, having been introduced in France in 1895. Habitually it is being rediscovered and optimistically brought forward as a sure-cure, generally by that man who "once had a case." Such favorable reports as are available seem to indicate that the beneficial results obtained are through antitoxic rather than bactericidal action. Often the results are similar to those of non-specific protein therapy. It is quite possible that worthwhile sera may yet be produced. To date, we are still waiting.

Non-specific therapy is a stepchild of vaccine therapy, and is dependent upon the effects of a generalized systemic reaction induced by some agent, such as a split protein. It is very difficult to assess honestly the value of this form of treatment, but we think it may be of use in low-grade chronic infections associated with little systemic reaction. It induces a leukocytosis, fever, and promotes phagocytosis. In virulent infection, when there is evidence of marked systemic reaction, its value is very dubious. A good preparation is 5 to 10 cc. of fat-free boiled milk given intramuscularly daily.

Blood transfusions are invaluable in sepsis. Used adequately and early, they combat shock and blood loss and often prevent sepsis, and once sepsis appears, counteract the anemia which rapidly develops. In a sense transfused blood acts as a non-specific agent and stimulates the reticulo-endothelial system of the recipient to increased cellular antigenic resistance. In combating active infections, it is our practice to give transfusions of 150 to 250 cc. of blood at intervals of two to four days. These are either direct or citrate, if the latter, the blood may be taken from a blood bank or if from a single donor, a large amount may be taken and kept to be distributed over a period of days in small amounts.

In our opinion specific immunotransfusions are of unusual value. We have seen enough favorable and occasionally startling responses to make us believe in their worth. Donors are so difficult to get and the bacterial strains so numerous however, that this is a little used therapeutic procedure. When the hemoglobin and red cell volume is high, as

seen by blood count and hematocrit determinations, then the cell-free serum of the specific blood may be used, in 150 to 250 cc amounts every other day. Otherwise, the whole blood is used.

### CHEMOTHERAPY

Chemotherapy in sepsis is the attempt to sterilize the blood stream and infected tissues of the patient by an injected or an ingested chemical agent. In years past, almost everything has been tried, and the optimistic claims for perennial cures leaves us doubtful and cynical.

The latest agents to gain attention are the derivatives of sulfanilamide and sulfanilamide itself. The first article in English by Colebrook and Kenny focused attention on the possibilities of specific chemotherapy in puerperal infections. Using prontosil and prontosil, now known as neoprontosil, Colebrook reported results not attainable with other forms of therapy. Since then, experiments and analyses by Long and Bliss, Brown, Fuller, Coman, Bannick, Lockwood, Coburn and others, have improved our understanding of the action, dosage and dangers of sulfanilamide and its compounds. Since sulfanilamide and neoprontosil are the two drugs in most common use, we will confine our discussion to these.

Seemingly these two drugs exert the same therapeutic effect. In addition, neoprontosil may be given intramuscularly to patients who are unable to take the drug by mouth. Recent experience with another sulfanilamide derivative, sulfapyridine, would tend to verify the existing belief that the action of neoprontosil is due to its own molecular constitution, rather than the amount of sulfanilamide which its reduction in the body liberates. Gross, Cooper and Lewis have indicated that neoprontosil has the ability to inhibit the hemolysin of hemolytic streptococci, while Huntington demonstrated that sulfanilamide exerted no such inhibition. Both drugs seem to inhibit growth and damage the organisms affected, permitting marked phagocytosis by leukocytes and later monocytes. The work of Long and Bliss indicates that this is true. Colebrook and Kenny demonstrated inhibition of the growth of the organisms themselves if the drug is given sufficiently early. Apparently there is no chemotropic effect and according to Coman the drug does not attract leukocytes. These drugs act as chemotherapeutic agents combating not only the organism but its toxic effect, but do not kill off directly the infectious organisms themselves. Organisms subjected to their effects lose virulence, and their growth is inhibited. Lockwood and

his co-workers believe that the drug interferes with the faculty of virulent hemolytic streptococci to obtain nitrogen from the serum protein or necrotic substances. Thus, we may say that while the exact mechanism of its antibacterial activity is not clearly known, and while end results of toxicity are yet to be resolved, sulfanilamide and its derivatives possess specific chemotherapeutic action upon certain bacteria. Neoprontosil seems to be tolerated somewhat better than sulfanilamide and is less toxic. Like sulfanilamide, it is rapidly excreted, about 90 per cent being eliminated in the urine within five hours of its administration.

The toxic symptoms ascribed to sulfanilamide and its derivatives appear to be caused by a sensitivity to the drug and an idiosyncrasy toward it. The symptoms are generally mild and are referable to the gastrointestinal and central nervous systems. Nausea, anorexia, malaise, dizziness, tinnitus and mental confusion are among the earliest symptoms noted. Cyanosis occurs in 25 to 50 per cent of cases after sulfanilamide ingestion, is much less frequently noted with neoprontosil and is rarely of moment. It is due in part to methemoglobinemia and sulfhemoglobinemia. Curtailment or temporary suspension of drug dosage leads to complete cessation of the symptoms. A progression of the symptoms leads to cramps and diarrhea, paresthesias, fever, abdominal and precordial pains, maculopapular skin rash, progressive anemia, hepatic or hemolytic jaundice, and granulocytopenia. These toxic symptoms are made worse by any existent renal or blood diseases or hepatic deficiencies. The blood count and blood smear must be watched and the drug discontinued if symptoms persist or recur, or if there is evidence of agranulocytosis. In our own experience, we had one case of agranulocytosis develop under sulfanilamide therapy with an eventually fatal outcome.

The organisms especially influenced are the hemolytic streptococci, gonococci, colon bacilli, and *B. melitensis*. Little effect seems to be noted in infections with *Streptococcus viridans*, hemolytic and non-hemolytic staphylococci, tubercle bacilli and pneumococci. The more recently developed sulfapyridine promises better results in some of these infections, notably against pneumococci.

Observation on the absorption and excretion of the drug indicates that an equilibrium can be established and a constant blood concentration maintained by repeating the drug dosage at four-hour intervals. A level of 5 to 10 milligrams per 100 cc. of blood is an optimum level for most infections. Long advocates a concentration of 10 milligrams per

100 cc of blood attained early and maintained until definite clinical improvement has been obtained or until toxic symptoms force discontinuance of the drug. More recently he has advocated even higher concentrations although in our experience it is extremely difficult to attain them. In milder cases effects may be obtained by administering 60 to 90 grains a day distributed in six doses at four-hour intervals. Another means for calculating dose is by the body weight, giving 15 grains daily for every 20 pounds of body weight in four or six doses. Thus the dose for a person weighing 160 pounds would be 120 grains or 20 grains every four hours. The usual dose of neoprontosil ranges from 5 to 15 grains every four hours. Both drugs preferably are given with the stomach relatively empty to avoid discomfort and nausea. When the blood sulfanilamide level can be followed, give relatively heavy doses at first in order to obtain the desired blood concentration, and then diminish the dose to the point at which the attained level may be maintained. When parenteral use of the drug is indicated, 0.8 per cent solution of sulfanilamide in physiologic saline solution is given, or neoprontosil solution 5 to 10 cc of a 2½ per cent solution intramuscularly every four hours. In calculating neoprontosil solution according to body weight, 1 cc of a 2½ per cent solution is given for each pound body weight up to 120 pounds which represents the maximum daily dosage. Again, this is divided into four or six injections a day. Clinical improvement may be expected within forty-eight hours, and the dosage commonly diminished thereafter. In using sulfanilamide or neoprontosil it is essential to continue treatment well beyond the time when the blood culture is negative and the patient seems free of infection. Disregard of this admonition will result in frequent recurrence and relapse.

In a two-year period, representing 10,830 deliveries, we had 464 cases morbid with pelvic infection. The majority were mild cases of endometritis subsiding under a regime which consisted of postural drainage, short wave therapy, oxytocics, avoidance of internal or external manipulation involving the uterus, and maintenance of the patient's general systemic condition with frequent use of blood transfusion. There were some cases of localized parametritis which responded satisfactorily to short wave therapy of the pelvis, foreign protein injections, bowel hygiene, pain relief and sedation.

Fifty patients were treated with sulfanilamide and there were four deaths in this group. Eleven patients had repeated positive blood cul-

tures, nine of which were hemolytic streptococci and one non-hemolytic. Eight of these ten patients with streptococcic septicemia recovered, a result which was not paralleled in our previous experience when sulfanilamide or neoprontosil were not available. All other forms of supportive therapy were used exactly as heretofore, this time in conjunction with these drugs. One of the deaths ascribed to peritonitis following hemolytic streptococcic septicemia did not have adequate sulfanilamide therapy. The total dose was only 320 grains and the drug was then stopped because the blood count dropped to less than 3,000 white cells. Other therapy was continued including repeated small blood transfusions totalling 1500 cc of blood over a period of ten days. The second patient to succumb with a hemolytic streptococcic septicemia was a 28-year old multipara admitted to the hospital in a desperate condition with postabortal sepsis after having had an abortion performed fourteen days earlier. The total amount given her was 125 grams (nearly 2,000 grains) of sulfanilamide given over a period of twenty days with a blood prontosil which ranged from four to as high as twenty, with the level being generally maintained at about 10 milligrams per 100 cc. She eventually died and at autopsy was found to have multiple lung abscesses. There was one patient with a positive *B. coli* septicemia who recovered. Of the thirty-nine patients whose blood cultures were either negative or not done, two died, one from an abruption of the placenta followed by cesarean section and peritonitis, and the second, from regional ileitis with postpartum intestinal obstruction, operation, and terminal peritonitis. The total sulfanilamide or prontosil dosage in the first case was 150 grains over ten days, and the second had neoprontosil solution 200 cc over a period of seven days. Obviously both of these dosages were inadequate. Judging from our experience in these fifty cases, it would seem best to give a heavy initial dose to attain an early therapeutic effect, give it early in the course of the disease, and maintain it, to avoid recurrence, until the patient gives clinicopathologic evidence of resistance or cure of the infection and is also symptomatically well. We have not before experienced such success in handling postabortal and postpartum sepsis associated with blood stream infections as has been our lot since using sulfanilamide and neoprontosil.

#### TREATMENT OF PYELITIS IN PREGNANCY

We have records of only sixteen cases of pyelitis of pregnancy



treated with sulfanilamide or neoprontosil. To evaluate it as a urinary antiseptic, it is necessary to determine whether the pyuria is an evidence of pyelocystitis or whether there is a coexisting pyelonephritis. The physiologic dilatation of the ureter with sluggish or absent peristalsis and atony, resulting in urinary stasis, makes pyelitis a common complication of pregnancy and one which is often treated with difficulty. Until recently our procedure has been to handle these cases conservatively with the standard urinary antiseptics unless the patient had a temperature and gastrointestinal symptoms, or seemed to have systemic disturbance as a result of infection. About six years ago we instituted ureteral catheter drainage for prolonged periods of two to seven days, with renal pelvic lavage. This treatment, combined with free use of transfusions to combat co-existing anemia, seemed to relieve most of our severe cases. With bacteriologic determination of the causative agent, urotropin seems sufficient for many cases of colon bacillus infections, although sulfanilamide is the best urinary antiseptic that we have encountered yet for other forms of organisms except *Streptococcus fecalis*.

With this last named organism, mandelic acid or ammonium mandelate seems to be most useful. A dosage of 45 to 60 grams of sulfanilamide a day is usually sufficient and will give a blood concentration of 3 to 4 milligrams per 100 cc of blood, according to Long and Bliss. This dosage of 10 grams every four hours is carried out day and night. Barr reports a series of sixty-four cases with cures of mild and severe forms of pyelitis in four to fourteen days using much smaller dosages. It is too early for us to evaluate our experiences with sulfanilamide and neoprontosil in pyelitis, although we may say at this time that we are favorably impressed with our results to date.

## PATHOGENESIS AND PRESENT DAY TREATMENT OF URINARY INFECTIONS\*

MEREDITH F CAMPBELL

INFECTION of the urinary tract is one of the commonest diseases of man, its recognition and successful therapy is a matter of everyday clinical concern. Etiology and pathogenesis must be appreciated if rational therapy is to be instituted. Only the high points of the clinical and therapeutic problem will be considered, theoretic considerations and controversial phases must necessarily be eliminated from the present discussion. In the treatment of these infections, the medication employed is often of secondary importance, rather it is essential that the accessory etiologic factors, which are predominantly obstructive, be recognized and adequately treated. Failure to recognize the existence and nature of these accessory factors accounts for most therapeutic failures. The introduction of mandelic acid, sulphanilamide and, in persistent staphylococcal infection, neoursphenamine has effectively relegated the formerly employed antiseptics such as methenamine, pyridium, acriflavine, caprokol, and methylene blue.

**ETIOLOGY** The bacterial invaders are conveniently classified according to their Gram-stain reaction. The Gram negative organisms are predominantly bacillary and of the colon-typhoid group. Of these, the *B. coli* *escherichia* is the commonest invading organism yet *B. lactis aerogenes* is of only slightly lesser incidence. Therapeutically it is extremely important to know which organism is present since *B. lactis aerogenes* is far more chemoresistant than *B. coli* *escherichia*. Gonococcal infections of the upper urinary tract are too rare to merit discussion here. The ammoniogenic *proteus bacillus* is encountered in 8 to 10 per cent of persistent urinary infections.

Of urinary tract invaders, the Gram positive staphylococci are outnumbered only by Gram negative colon bacilli and bacteriologic studies made during the initial stages of acute urinary infection have sometimes

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indicated an even higher incidence of staphylococci than colon bacilli. In urinary infection the albus and aureus varieties of staphylococcus are of equal importance and pathogenicity. Streptococci are found in about a third of all cases of mixed urinary infection. The beta hemolytic variety is usually readily susceptible to sulphanilamide therapy.

The accessory etiologic factors in urinary infection merit scarcely less attention than the bacterial invaders themselves. Lesions which cause urinary stasis or urinary constipation are of greatest importance. It should be distinctly understood, however, that urinary infection may occur, and commonly does, in the absence of urinary obstruction. Yet here the infection usually disappears readily and is most unlikely to become a serious therapeutic problem.

Obstructive lesions in adults are generally acquired, but in children are usually associated with congenital malformation. The obstruction may be transient, as observed during pregnancy, at which time uterine compression of the ureters as they cross the bony pelvis produces urinary back pressure with dilatation of the upper urinary tract. Here the introduction of bacteria or the revivification of existent organisms is commonly followed by clinically important urinary infection. Therapeutically, recognition of the improper urinary drainage and its correction by the indwelling ureteral catheter, may usually be relied upon to bring these patients through normal and satisfactory delivery. In an eight weeks old girl I examined because of persistent acute "pyelitis," urologic investigation disclosed an infected hydronephrosis secondary to congenital right ureteropelvic junction stricture. Passage of the catheter coincident to urologic examination restored urinary drainage sufficient to cause the temperature to drop to normal in 24 hours. These citations illustrate the importance of considering and treating the associated etiologic lesions in urinary infections of all varieties.

*Routes of invasion.* In discussing infections of the urinary tract the infection is assumed to be predominantly renal. Yet we know that sometimes the urinary infection which is commonly, loosely and inadequately designated pyelitis, is confined to the lower urinary tract. Here the infection doubtless enters through the urethra. On the other hand, the "cystitis" myth should be laid. Cystitis as an independent lesion is practically unknown, in most cases thus diagnosed because of urinary disturbances, the vesical inflammation is secondary to renal infection, known or unrecognized, or to posterior urethral or prostatic

inflammation with or without infection. When "cystitis" exists, consider it secondary to renal infection until proved otherwise.

In most urinary tract infections the invading bacteria reach the kidney through the blood stream or by lymphohematogenous invasion from a primary focus elsewhere. In direct hematogenous infection the organisms are usually derived from an enteric, cutaneous, respiratory, or dental focus, yet the bacteria may be present as etiologic factors in a specific systemic disease such as typhoid. In lymphohematogenous invasions of the kidney, the primary focus is frequently in such pelvic organs as the Fallopian tubes, seminal vesicles, or prostate. The bacteria are absorbed by and transported through the lymphatics, reaching first the lower regional pelvic lymph nodes and passing thence into the thoracic duct and general circulation.

**PATHOLOGY** Convincing experimental evidence indicates that the kidney is not a bacterial filter, bacteria cannot pass the epithelial barrier of the renal collecting system without producing tissue injury even though the injury cannot be later histologically demonstrated. This point is of vast importance in the consideration of renal bacteriuria, the demonstration of which must be accepted as indicative of bacterial kidney injury, predominantly of the cortex.

The terminology of urinary infection merits brief consideration. As previously indicated the term pyelitis has been loosely applied to all varieties of urinary tract infection. In the usual renal infection the pathologic picture is that of an interstitial suppurative pyelonephritis in which the parenchymal lesion is of grave importance while the pelvic lesion is generally negligible. Yet there are several pathologic conditions which may clinically simulate so-called acute pyelitis or acute pyelonephritis. The more important of these conditions are

**Bacteriuria** In this condition the urine is usually hazy or opalescent with bacteria and if bacillary organisms predominate, the condition is designated as a bacilluria. Pus cells are few in number and often are entirely absent. In bacteriuria, the infection is commonly confined to the lower urinary tract yet the likelihood of upper urinary tract involvement cannot be disregarded. In bacteriuria, the institution of free urinary drainage, and the liberal administration of the newer antiseptics will usually sterilize the urinary tract.

**Pyelitis** Renal infection limited to the pelvis has not been satisfactorily demonstrated in the human being. It has been observed during

the first few hours of experimental renal infection, especially of the ascending variety. Yet after two days it has been impossible to determine histologically whether the animal's renal infection was ascending or hematogenous. I strongly feel that until an adequate examination has been made, it is more proper to designate the condition as an acute or chronic urinary infection than to attempt a specific and pathologically undemonstrable diagnosis, such as pyelitis.

*Pyelonephritis* This is the usual lesion in acute renal infection. Histologically it is characterized by myriads of interstitial suppurative processes, usually bilateral and universally distributed. Cortical involvement is generally more pronounced than medullary. The bacterial invasion is customarily through the blood vessels, but may be through the lymphatics. In either event the interstitial leukocytic infiltration and suppurative process are characteristically perivascular. Mild lesions may heal with neither clinical manifestations nor scarring. In advanced suppurative nephritis productive of symptoms, a variable reparative renal scarring must be expected. During the evolution of the suppurative process, there is cloudy swelling of the adjacent renal tubules and in serial section polymorphonuclear leukocytes can be demonstrated extruding their way from the interstitial lesion and between the swollen tubular epithelial cells into the lumen of the collecting tubules. Thus it is that most of the pus demonstrated in the urine of patients with renal infection originates in the interstitial suppurative process in the parenchyma rather than in the kidney pelvis or lower urinary tract.

As a therapeutic corollary excretory antisepsis can be effective only as the drug hematogenously reaches the suppurative focal infections in the kidneys. Chemotherapy may fail when the renal function is greatly depressed and the concentration of the drug excreted is bacteriostatically ineffective. Moreover, when urinary stasis exists, the congested, inflamed renal parenchyma involved by the urinary stagnation or back pressure is less able than normal to cope with the existent infection. Yet with the institution of free drainage, rehabilitation of the local renal defensive mechanism, and excretory antisepsis the bacterial invasion is usually readily controlled and often cured.

*Infected hydronephrosis* The obstruction which causes the hydronephrosis is usually at the outlet of the renal pelvis but may be at any distal point. The renal changes are those of hydronephrotic back pressure injury plus the suppurative lesions described under pyelonephritis.

Yet the establishment of free drainage reinforced by chemotherapy will frequently overcome the renal infection. Sometimes the urinary obstruction in infected hydronephrosis can be eliminated only by surgical plastic procedure but in advanced disease nephrectomy may be required.

*Pyonephrosis* This may be the end stage of an infected hydronephrosis in which generalized suppurative destruction of the kidney occurs or it may be a massive suppurative renal destruction without demonstrable obstruction. In any event, the kidney is functionally dead, an active toxigenic focus, and must be treated by removal rather than by chemotherapy.

Surgical treatment, usually nephrectomy, is life saving in certain acute massive hematogenous suppurative renal lesions such as the pyemic kidney, in the localized hematogenous suppurative lesion commonly designated as renal carbuncle, and in perirenal abscess which is predominantly hematogenous and staphylococcal in origin.

**SYMPTOMS** The clinical picture of acute urinary infection is well known and the diagnosis is usually correctly made, even though the accessory factors may be inadequately comprehended. In acute urinary infection the general symptoms are most prominent, a third to a half of adults will suffer no symptoms pointing to the urinary tract. The onset is usually abrupt with chills, fever, malaise and gastrointestinal disturbances, in the initial stages and lacking symptoms referable to the urinary tract, the usual diagnosis is gripe. In most urinary infections the manifestations of the acute stage disappear in seven or ten days yet the urine usually continues to show pus for a month or longer. Gastrointestinal disturbances will be outstanding in approximately half of patients with chronic urinary infection. With advanced renal injury neurologic manifestations—irritability, lethargy, forgetfulness, and stuporousness—may appear. Persistence of renal infection, acute or chronic, means increased pathologic severity and must definitely influence treatment.

No patient should be discharged as cured until at least two negative cultures of a catheterized specimen have been obtained.

**DIAGNOSIS** The history of sudden onset, chills, gastrointestinal and vesical disturbances perhaps with pain in the renal region, at once suggests acute urinary infection. The diagnosis is confirmed by urinalysis in which we are particularly interested in the pus, blood and

bacterial content of the urine Pus casts at once indicate pyelonephritis In some instances pyuria and urinary infection are accidental findings in urinalysis coincident with physical examination or examination for some other condition This is particularly true in children

In the study of urinary infection, the method of specimen collection is paramount and in the female only specimens collected by catheterization are worth examining External scrubbing of the introitus and external urethral meatus as a substitute for catheterization causes far more trauma than urethral catheterization and is bacteriologically inadequate In the male, a satisfactory specimen for culture can be obtained if, after wide retraction of the prepuce, the glans and meatus are well sponged with an antiseptic solution, such as bichloride or oxycyanide of mercury 1:500, after which the patient passes a small amount of urine before voiding into a sterile receptacle Unless the specimen can be collected in this manner from the male, catheterization must be employed I have several times examined female patients referred for urological examination because of so-called chronic pyelitis and in whom the laboratory had always reported a grave pyuria which was subsequently determined to be of vulvar origin, catheterized specimens, previously not taken from these patients, were normal and sterile I have also had a similar experience in young males with a tight prepuce in whom subpreputial debris collected in the voided urine had been misinterpreted in terms of renal infection Circumcision was curative

It must be recognized that failure to demonstrate pus does not rule out grave renal infection This is best illustrated in renal carbuncle and perirenal abscess Here the renal suppuration does not drain into the collecting tubules to appear as pus in the bladder urine, yet culture of this urine will regularly disclose the invading organism These conditions and pure bacteriuria are perhaps the best examples of apyuric urinary infection

When the acute urinary infection remains acute for longer than five to six days despite intensive therapy a urologic examination is indicated In such cases obstruction or suppuration requiring instrumental drainage or surgical incision will usually be found In some instances, the temperature following acute urinary infection does not come down to normal but remains at 99° or 99.2° F Urinalysis will demonstrate that urinary infection persists Failure to cure these patients by intensive medical treatment over a period of three to four weeks demands a

comprehensive urologic examination at which time the accessory etiologic factors will be demonstrated. Yet in chronic urinary infection successfully eradicated by the newer chemotherapy, the previous persistence of the infection strongly suggests that urinary stasis exists and these patients are entitled to an excretory urographic investigation before being discharged. In a surprising number, unsuspected obstructive uropathy will be demonstrated.

**PROGNOSIS** The importance of urinary infection in the young may be deduced from the death incidence of a fifth to a third in infancy and approximately 3 per cent in older children. In infants failing nutrition doubtless accounts for more deaths than bacterial toxemia *per se*. This indicates the therapeutic importance of maintaining nutrition in young patients with urinary infection. Adults rarely die from uncomplicated acute pyelonephritis but complicating or secondary pyonephrosis, perinephritic abscess, renal carbuncle, or pneumonia, for example, may be fatal. In short, the prognosis in urinary infection depends upon the severity of renal injury, the accessory etiological factors, extraordinary complications and the treatment.

**TREATMENT** In the therapeutic management of urinary infection, we disagree with those who rush at once for the medicine bottle. These patients merit sickroom quiet and rest in bed until the temperature has been normal for forty-eight hours. Renewed fever on getting up calls for further bed rest.

There is no special diet. Easily digestible foods may be given, as the patient improves, the appetite will return. Only in infants is the maintenance of nutrition likely to be of vital importance. During the acute stage of the infection a high fluid intake is essential to promote diuresis and combat dehydration, an approximate intake of one ounce of fluid per pound of body weight is desirable. This may be given by mouth, hypodermoclysis or intravenous infusion, the addition of glucose in 5 to 10 per cent volume concentration helps to combat acidosis, the clinical manifestations of which so commonly predominate in the general symptomatology of acute urinary infection, especially in children. For the same reason the administration of an alkali such as sodium bicarbonate is rational.

It is usually extremely difficult to identify the primary bacterial focus of infection in urinary infection hence the therapeutic eradication of the focus is rarely accomplished.



In the detoxication of the patient intestinal evacuation will be more effective than any other single measure. In carrying this out mild catharsis with a saline compound or castor oil is reinforced by colonic irrigations given once or twice daily during the acute stage of the infection and at longer intervals as the infection subsides. The volume of tap water used for the colonic is more important than the fecal return, for a colonic irrigation in an adult we advocate the use of at least eight gallons of water. A competent nurse should be able to administer this much fluid without seriously disturbing the patient. The first day or two the return from the irrigation may be clear or contain only strings of mucus and relatively small amounts of fecal debris, but about the third or fourth day an amazing amount of feces will be recovered and coincident with this increased evacuation, the patient will show pronounced improvement.

**CHEMOTHERAPY** In recent years the chemotherapy of urinary infection has undergone revolutionary changes. Many methods and drugs formerly extensively employed have been largely discarded. Alkalinization of the urine by the administration of sodium bicarbonate is effective only to the extent that the medication combats acidosis, the urinalysis indicates no improvement. Therapeutic urinary acidification *per se* is seldom successful but is invaluable in combination with methenamine or mandelic acid ingestion. The empiric changing of the urine reaction from acid to alkaline and vice versa is valueless. Caprokol, pyridium, methenamine, methylene blue and other so-called urinary antiseptics which formerly enjoyed wide use, during the past three years have been largely replaced by mandelic acid and sulphanilamide, and in the present discussion of chemotherapy only the last two drugs and neoarsphenamine will be considered.

The choice of urinary antiseptic will be guided by the bacterial invader, the renal function of the patient, and his drug tolerance. As a rule, the renal function permitting, mandelic acid is my first choice in the treatment of urinary infections, chiefly because of lesser toxicity than sulphanilamide. Yet we have no quarrel with those who prefer sulphanilamide when bacteriologically indicated. We employ neoarsphenamine for staphylococcal infections which respond neither to mandelic acid nor to sulphanilamide.

**MANDELIC ACID** This chemical is bactericidal against most of the common urinary tract bacterial invaders when the urinary pH is 5.5

TABLE  
SULPHANILAMIDE AND MANDELIC ACID THERAPY  
FOR URINARY INFECTIONS

<i>SULPHANILAMIDE</i>		<i>MANDELIC ACID</i> (ammonium or calcium salt)	
DOSE (IN 24 HOURS)			
<i>Grains</i>	<i>Grams</i>	<i>Grains</i>	<i>Grams</i>
Under 2 years 5-10	3 - 6	Under 2 years 30- 60	2- 4
2- 4 years 10-20	6 -12	2- 4 years 60- 90	4- 6
5- 8 years 15-25	9 -15	5- 8 years 75-120	5- 8
9-12 years 20-25	12 -15	9-12 years 120-180	8-12
Adults 25-80	15 -48	Adults 180-225	12-15
Average dose (Per 10 Pounds Body Weight)	5	18.75	1.25

## BACTERIOLOGIC INDICATIONS

Gram negative bacilli  
(*B. coli* escherichia,  
*B. lactis* aerogenes,  
*B. typhosus*)

*Staphylococcus*

*Streptococcus hemolyticus*

*Proteus*

*Procyaneus* (*pseudomonas*)

Gram negative bacilli  
(*B. coli* escherichia,  
*B. lactis* aerogenes,  
*B. typhosus*)

*Staphylococcus*  
*Streptococcus*, hemolytic  
and non-hemolytic

*Enterococcus* (*Streptococcus*  
*fecalis*)

*Procyaneus* (*pseudomonas*)

## INEFFECTIVE AGAINST

*Enterococcus* (*Streptococcus*  
*fecalis*)

*Proteus* (unless urine highly  
acid)

## FLUID INTAKE

Restrict to 1200 cc in 24 hours in adults  
Restrict only with great caution in children

## URINE REACTION\*

Preferably alkaline, coadminister  
sodium bicarbonate, or potas-  
sium citrate q.s.

Must be more acid than pH 5.5  
Mandelic acid concentration greater  
than 0.5 per cent  
Give Ammonium chloride  
Ammonium nitrate  
Dilute hydrochloric acid q.s.

\* Best estimated by potentiometer or nitrazene solution or paper

or less and the concentration of the mandelic acid in the urine is 0.5 per cent or greater. The bactericidal action is usually regularly satisfactory when the pH is 5.2 and the acid concentration 0.8 per cent or greater.

Mandelic acid excreted in the urine may produce renal irritation and for this reason is contraindicated when noteworthy renal disease or injury exists. This irritation may be manifested by desquamation of renal epithelial cells, by hematuria and the passage of casts. Moreover, in cases of important renal disease, the damaged kidney frequently fails to excrete mandelic acid in amounts sufficient to be bactericidal. Thus the therapeutic course is not only unsuccessful, but mandelic acid may accumulate to a dangerous degree (acidosis) in the body. For these reasons, the approximate renal function should be known before administration of mandelic acid is begun. In cases of serious renal injury sulphanilamide should be chosen rather than mandelic acid, bearing in mind that inadequate excretion of the sulphanilamide may also render its use ineffective and its cumulative retention in the body may become a serious toxic factor.

Mandelic acid salts are marketed chiefly in the ammonium variety as tablet, elixir, or syrup, yet I prefer the calcium mandelate tablet, especially since I have found it more easily administered to young children and with less disturbance than other mandelic acid preparations. The basis of drug computation I usually follow is that of approximately 2 grains of the salt per pound of body weight in 24 hours. In most instances the mandelic acid salt will sufficiently acidify the urine but should the pH not be below 5.5 after 48 hours of mandelic acid administration, an acidulating salt such as ammonium chloride, calcium chloride, ammonium nitrate, or dilute hydrochloric acid should be administered at the same time in sufficient quantity to bring about the desired urinary acidity. The urinary pH may be estimated approximately by the use of nitrazene test papers which are checked against a standard colorimetric scale. Because adequate urinary acidulation must be absolute for the successful employment of mandelic acid therapy, the titre of the urine should be estimated once and preferably twice daily during the therapeutic period.

The mandelic acid compound is administered for a period of eight to ten days, meanwhile periodic reexaminations of the urine are made. In successful cases the urine is often pus free by the fourth or fifth day.

Yet one should not rely on cultures made while the patient is taking the urinary antiseptic, since its bacteriostatic activity in the collected specimen may be sufficient to inhibit growth and render the culture sterile. However, if the therapeutic progress is favorable, we wait three to four days after stopping the medication and take an aseptically collected specimen for culture. If no growth is obtained in 72 hours, a similar specimen is subsequently taken and if two negative reports are obtained, the patient is discharged as cured to return in one month for a final bacteriologic check up. If this test of cure is regularly followed, the incidence of so-called "recurrences of pyelitis" will be vastly diminished. Most alleged recurrences are simply exacerbations of smoldering, unrecognized infections persisting after the clinical disappearance of an infection previously acute. These exacerbations usually follow the onset of acute focal infection elsewhere, such as rhinitis, bronchitis or enteritis.

If the intensive administration of mandelic acid for eight to ten days is unsuccessful and if bacteriologic indications permit, it is my practice to switch the patient to sulphanilamide therapy for a similar period.

**SULPHANILAMIDE** Sulphanilamide is effective against the common Gram negative invaders of the urinary tract including the proteus bacillus, and also against most of the Gram positive cocci. Yet it is ineffective against the enterococcus (*S. faecalis*), an organism we have found in about 3 per cent of urinary infections in children.

The average dose of sulphanilamide is about 5 grains for 10 pounds of body weight, yet in young children I have frequently used doses disproportionately larger. Sulphanilamide acts best in an alkaline medium, sodium bicarbonate or other alkalinizing agent is administered between meals (so as not to interfere with digestion) in doses adequate to render the urine strongly alkaline. Because of this superior activity in an alkaline urine, sulphanilamide is usually readily effective against the proteus bacillus which by its ammoniogenic activity regularly produces extremely alkaline urine.

I do not believe we are justified in persisting with intensive administration of sulphanilamide for longer than eight to ten days at a time, although I am aware that many clinicians not only give larger doses than have been indicated here but for much longer consecutive periods. My respect for the potential toxic properties of sulphanilamide is ever increasing. It is recognized that cyanosis in itself is of little clinical

importance Yet one cannot always identify hematologic changes in time to prevent serious injury I have recently experienced this in an adult who received only 25 grains (5 grain doses) of sulphanilamide during a 36 hour period Yet during this time his previously normal blood count was reduced to 1,800,000 red cells per cmm, the leukocytes to less than 2,000 per cmm, the hemoglobin to less than 40 per cent, an acute hemolytic crisis occurred, and after three transfusions totaling nearly 2,000 cc of blood, the patient's blood count was still 25 per cent below normal

Apparently there is little difference in therapeutic activity of sulphanilamide and di-sulphanilamide in the urinary tract During the past two months we have been studying the therapeutic effect of sulfapyridine in urinary infections in children but as yet can offer no conclusions

**NEOARSPHENAMINE** It has become more generally appreciated of late that staphylococcal infections of the urinary tract often will readily respond to the intravenous injection of neoarsphenamine when given in the same manner as in the treatment of syphilis Urinary sterilization will commonly be accomplished with four injections and if six injections are fruitless, more should not be given I have employed intravenous neoarsphenamine only as a last resort in the treatment of staphylococcal infections, largely because of the objections raised by intelligent patients who are keenly aware of its usual antiluetic application In fact, in my experience its employment in the treatment of urinary infections in private practice requires considerable explanation to the patient

If the acute urinary infection does not show definite response to intensive medical therapy as above outlined within one week, a urological investigation is indicated, as it is in chronic urinary infection not responding to intensive medical treatment for one month Such urologic investigation nearly always will demonstrate some form of urinary obstruction as the principal accessory agent It must be remembered that neuromuscular disturbances of the urinary tract — commonly designated as cord bladder — produce urinary stasis by engendering expulsive inertia with consequent stagnation This condition invites urinary infection and perpetuates infection already established

**RESULTS** Two-thirds of non-tuberculous urinary infections can be eradicated by medicinal means In the remaining third additional treatment will be employed according to etiologic indications This may

mean, for example, conservative instrumental dilatation of a urethral or ureteral stricture, or the radical removal of a stone from a kidney, or perhaps nephrectomy. Thus in the diagnostic investigation of chronic urinary infection in children we have demonstrated practically every urologic lesion known to exist in the adult.

**RENAL TUBERCULOSIS** It is notable that chronic caseous tuberculosis exists in about one in sixty cases of persistent pyuria in children, and in adults its incidence is even greater. The treatment of unilateral renal tuberculosis is surgical, yet the demonstration of tubercle bacilli apparently passed from a kidney which shows a normal pyelogram does not call for nephrectomy. Nephrectomy should be reserved for those organs in which a tuberculous process is urographically demonstrable. Bilateral renal tuberculosis is a sanatorium medical problem offering a hopeless prognosis.

**SUMMARY** The clinical phases of urinary infection have been briefly discussed. The etiology and pathogenesis are of utmost importance in the rational selection of treatment. If one relies on medical therapy alone, his results will be far less satisfactory than those of the clinician who thinks first in terms of potential accessory etiologic factors, and notably obstruction, and secondarily considers chemotherapy. The choice between mandelic acid and sulphanilamide should rest first upon specific bacteriologic indication and secondly upon renal function and tolerance of the patient for the drug. With intelligent chemotherapy, about two-thirds of the common urinary tract infections can be cured. In the remainder, instrumental or surgical treatment must be combined with medicinal therapy.

## LIBRARY NOTES

### AN EXHIBITION OF BOOKS ON THE GROWTH OF OUR KNOWLEDGE OF BLOOD TRANSFUSION\*

Prepared by

GERTRUDE L. ANNAN

In Charge of the Rare Book and History Rooms

#### EARLY REFERENCES TO BLOOD TRANSFUSION

- 1 Ovid 43 B C-18 A D  
Metamorphoses with an English translation by Frank Justus Miller  
London, 1929, opened at vol I, pp 366-367  
Medea said "Come, draw your swords, and let out his old blood that I may refill his empty veins with young blood again"  
Borrowed through the kindness of the New York Public Library
- 2 [A modern account of what has been called the first operation of blood transfusion]  
In Villari, Pasquale *Life and times of Girolamo Savonarola*, London, [1918], opened at p 151  
This account of the blood of three young boys being given to the aged Pope Innocent VIII, 1432-1492, claims that the blood was injected into the veins, but there seems to be no proof of this. Another version states that the blood was offered as a drink to the Pope who refused it.  
See Ogle, *Harzeian oration*, London, 1881, note 20, p 107
- 3 Ficinus, Marsilius 1433-1499  
*De triplici vita*  
Florence, 1489, opened at folio 3r  
This Italian philosopher suggests the giving of healthy young blood from the veins of the arm to the aged by means of suction
- 4 Pegel, Magnus 1547-ca 1615  
*Thesaurus rerum, selectarum, magnarum, dignarum, utilium*  
[Rostock], 1604, opened at p 112  
A reference to a "rare surgical operation," which has been thought to be that of blood transfusion, although the account is so vague that the precise nature of the operation cannot be determined. The author of this very rare work was a physician and mathematician.  
Borrowed through the courtesy of the Preussische Staatsbibliothek, Berlin, Germany
- 5 Libavius, Andreas ca 1546-1616  
*Appendix necessaria syntagmatis arcanorum chymicorum*  
Frankfort, 1615, opened at p 8  
This seems to be the earliest account of blood being transfused directly from the arteries of one man into the arteries of another. The author was an eminent German chemist and physician.  
Borrowed through the courtesy of Princeton University Library

\* Prepared in connection with the Graduate Fortnight on Diseases of the Blood and Blood-forming Organs held at The New York Academy of Medicine Oct 24 to Nov 4 1938

FRENCH CONTRIBUTIONS TO BLOOD TRANSFUSION IN THE SEVENTEENTH CENTURY

- 6 Denis, Jean Baptiste d 1704  
Lettre escrete a [Habert] de  
Montmor touchant une nouvelle  
maniere de guerir plusieurs maladies  
par la transfusion du sang  
[Paris, 1667], opened at pp 12-13  
An account of the first transfusion of  
blood from animal to man, performed  
June 15th, 1667 Denis was involved for  
years in controversy on the subject of  
transfusion and its dangers  
Photostat copy from the Bibliotheque  
nationale
- 7 Lamy, Guillaume fl 1672  
Lettre escrete a [Jean Baptiste]  
Moreau contre les pretendues utilites de  
la transfusion du sang  
[Paris, 1667]  
A response to Deniss arguments for  
blood transfusion, dated July 8, 1667  
Photostat copy from the Bibliotheque  
nationale
- 8 Petit, Pierre 1617-1687  
De nova curandorum morborum ratione  
per transfusionem sanguinis  
Paris, 1667  
A tract against transfusion by the phy-  
sician and Latin poet, July 11, 1667  
Photostat copy from the Bibliotheque  
nationale
- 9 Gadois, Claude d 1678  
Lettre escrete a l'abbé Bourdelot  
pour servir de reponse au Sr Lamy,  
& confirmer en mesme temps la transfu-  
sion du sang par de nouvelles experi-  
ences  
[Paris, 1667]  
A reply to Lamy in behalf of blood  
transfusion written August 8th 1667,  
by the young scholar who became direc-  
tor of the military hospital at Metz and  
died at the age of thirty-six  
Photostat copy from the Bibliotheque  
nationale
- 10 Tardü Claude 1607-1670  
Traite de lecoulement du sang d'un  
homme dans les venes d'un autre  
Paris, 1667  
The first account of the technique of  
direct transfusion of blood from one  
man to another While Denis was trans-  
fusing the blood of animals into man,  
Tardü published this detailed account of  
his technique in direct transfusion  
There is no proof, however, that he put  
his theories into practice
- 11 de Gurye, Gaspard fl ca 1668  
Lettre a M l'abbé Bourdelot  
touchant la transfusion  
Paris, 1667  
In *Le journal des sçavans de l'an M  
DC LXVIII* Amsterdam, 1679, opened  
at p 313  
A contemporary review of the work by  
Gurye which contains the "first warning  
of the dangers attending the administra-  
tion of incompatible blood" (Kevnes)  
An English account is found in *Philo-  
sophical Transactions abridged*  
London, 1809, vol 1, p 183 Gurye notes  
both the advantages and evils of blood  
transfusion
- 12 De la Martiniere, Pierre Martin 1634-  
1676  
Les opuscles contre les circulateurs  
& transfuseurs de sang  
Paris, [1668]  
Another tract against transfusion writ-  
ten by the surgeon and traveler, with  
royal privilege to print dated June 16,  
1668  
Photostat copy from the Bibliotheque  
nationale
- 13 de Basril, Louis fl ca 1667  
Reflexions sur les disputes qui se  
font a l'occasion de la transfusion  
[Paris, ca 1668]  
Transfusion is championed by a layman,  
an "avocat en Parlement," who criti-  
cizes Lamy and De la Martiniere for  
their attacks upon it  
Photostat copy from the Bibliotheque  
nationale
- 14 Sentence rendue au Chastelet par Mon-  
sieur le lieutenant criminel le 17 avril  
1668  
In *Ors, P C Études historiques  
sur la transfusion du sang* 2 ed PARIS,  
1876, pp 42-44  
This decrees that in the future blood



transfusion cannot be done upon man without the permission of a physician of the Paris faculty, which had heartily opposed transfusion. The sentence was brought about at the instigation of a widow of one of Denis's patients. The patient, insane, had been treated by transfusion and considerably helped, but later died. The widow was aroused to action by Denis's adversaries.

- 15 France Arrêt du Parlement de Paris du

10 janvier, 1670

In Villaret, Maurice et Montier, François "Les origines de l'injection thérapeutique intra-veineuse"

In *Paris médical*, 1921, vol 42, (annexe), opened at p 120

This Arrêt which forbids all doctors to practice blood transfusion is apparently not now in existence. The authors of the article give here the extant references to it.

#### ENGLISH CONTRIBUTIONS TO BLOOD TRANSFUSION IN THE SEVENTEENTH CENTURY

- 16 Oldenburg, Henry 1615?-1677  
An account of the method of conveying liquors immediately into the mass of the blood

In *Philosophical transactions of the Royal Society of London* [for the year 1665] abridged London, 1809, p 45

Oldenburg, secretary of the Royal Society and editor of its *Transactions*, reports the discovery of this new experiment by the well known architect, Christopher Wren, 1632-1723. The Italian physician, Folli, later claimed that Wren had learned it from him.

- 17 Lower, Richard 1631-1691

*Tractatus de corde*

Amsterdam, 1669, opened at p 181

Description of his technique of blood transfusion by the English physiologist who was the first in that country to perform the transfusion of blood from one animal to another, in February, 1665.

- 18 Boyle, Robert 1627-1691

The method observed in transfusing the blood out of one animal into another

In his *Works* London, 1772, vol 3, pp 149-151

The great scientist's account of Lower's experiment appeared in the *Philosophical Transactions* for December 17, 1666.

- 19 Lower, Richard 1631-1691, and King, Sir Edmund 1629-1709

Transfusion practised upon man

In *Philosophical transactions abridged and dispos'd under general heads* by John Lowthrop London, 1705, vol 3, p 231

Record of the first human transfusion in England on November 23, 1667. Sheep's blood was used. The *Philosophical Transactions* of the period contain accounts of the many experiments in England and elsewhere.

- 20 Pepys, Samuel 1633-1703

The diary with Lord Braybrooke's notes edited by Henry B. Wheatley

London, 1895, vol 6, opened at p 67

The famous diarist made several references to the transfusion experiments. In this one he mentions the opinion of the scientist, Robert Hooke, 1635-1703.

#### CONTRIBUTIONS OF COUNTRIES OTHER THAN ENGLAND AND FRANCE IN THE SEVENTEENTH CENTURY

- 21 Folli, Francesco 1624-1685

*Stadera medica nelle quale oltre la medicina infusoria e le contrario alla trasfusione del sangue*

Florence, 1680, opened at p 35

This Italian physician claims that after reading Harvey's work on circulation in 1652 he saw the possibilities of transfusion and in 1654 conducted experi-

ments before Ferdinand, Grand Duke of Tuscany. He claims further that the English scientists heard of his experiments, but gave him no credit for the discovery.

- 22 Major, John Daniel 1634-1693

*Chirurgia infusoria*

Kiel, 1667, opened at p 2

A contemporary illustration depicting

- the operation of the injection of medicines into the veins On p 212 of this work, the author describes blood transfusion
- Borrowed through the courtesy of the Army Medical Library
- 23 Ettmuller, Michael 1644-1683  
Dissertation sur l'infusion des liqueurs dans les vaisseaux  
In his *Nouvelle chirurgie* Lyons, 1691, opened at p 511  
Published first in 1668, this contains a recommendation for the infusion of human blood in the veins in the treatment of fevers
- 24 van Lamsweerde, Jan Baptist fl ca 1700  
Appendix ad Armamentarium chirurgicum  
In Scultetus, Joannes *Armamentarium chirurgicum* Levden, 1693  
This contemporary illustration of the technique and instruments used in blood transfusion appeared first with the 1672 edition of Scultetus
- 25 Bartholinus, Caspar (the younger) 1655-1738  
De chirurgia transfusoria  
In Bartholinus, Thomas (the elder) *Acta medica et philosophica* Copenhagen, 1677, vol 3, p 86  
A note on transfusion from Paris by the well known Danish physician "Transfusion underwent in Denmark the same fortune as in France and Italy, meeting there likewise with its adversaries, who brought it into discredit" (Ullersperger)
- 26 Mercklin, Georg Abraham 1644-1702  
Tractatio med curiosa, de ortu & occasu transfusionis sanguinis  
Nuremberg, 1679  
One of the most violent attacks on blood transfusion by a prominent German physician, who includes here a history of the subject
- 27 Nuck, Antonius 1650-1692  
Operationes et experimenta chirurgica  
Ieyden, 1733, opened at p 166  
Originally published in 1692, this advises the use of blood transfusion in a number of diseases, and complains that the operation has been neglected for some years
- 28 Purmann, Matthaus Gottfried 1648-1721  
Chirurgia curiosa or, the newest and most curious observations and operations in the whole art of chirurgery  
London, 1706, opened at p 304  
A description of transfusion by the eminent military surgeon, published originally in 1694 Purmann regrets that the operation was not then in general use and cites a case of leprosy which he cured by transfusion

# BLOOD TRANSFUSION IN THE EIGHTEENTH CENTURY

- 29 Heister, Lorenz 1683-1758  
A general system of surgery  
London, 1743, opened at vol 1, p 305  
The great German surgeon of the eighteenth century describes the operations of transfusion and infusion which 'are seldom practised by our modern surgeons, yet they were highly celebrated, and often performed, in the last century, from the year 1660-1680 "  
His work appeared in 1719
- 30 Rosa, Michele 1731-1812  
Lettere estemporanee sopra alcune curiosita fisiologiche  
[Napoli], 1782, opened at p 80  
Inaugural dissertation
- Rosa's successful experiments on animals in February, 1783, were the first to be presented to the medical profession in many years
- 31 Harwood, (Sir) Busick 1745-1814  
[Account of his experiments in blood transfusion]  
In *Philosophical transactions of the Royal Society of London abridged*  
London 1809, p 185, note Photostatic copy  
Harwood was the first to revive interest in blood transfusion in England by his successful experiments on dogs in 1785
- 32 Seibert, Adam 1773-1825  
An attempt to disprove the doctrine of

the putrefaction of the blood of living animals

Philadelphia, 1793, opened at pp 54-55  
A series of experiments of an American physician who injected putrid blood into the veins of animals, to determine its effect upon normal blood

33 Darwin, Erasmus 1731-1802

*Zoonomia, or, the laws of organic life*  
2 ed London, 1796, opened at vol 2, p 605

The famous physician and botanist suggests the use of transfusion in fevers, and describes the operation

#### BLOOD TRANSFUSION IN THE NINETEENTH CENTURY

34 Scheel, Paul 1773-1811

*Die Transfusion des Blutes*

Copenhagen, 1802, opened at p 11

This excellent history of transfusion was compiled at a time when that method of treatment was seldom used and infrequently mentioned. The careful bibliography has been of inestimable value to those interested in the early history of the subject.

35 Prevost, Jean Louis 1790-1850, and Dumas, Jean Baptiste Andre 1800-1884  
*Physiologie animale. Examen du sang et de son actions [sic] dans les divers phenomenes de la vie*

In *Bibliothèque universelle des sciences* Geneva, 1821, vol 17, opened at pp 226-227

Although these experimenters had some success in bringing back to life by blood transfusion a horse which had been bled to syncope, their conclusions were that the operation was dangerous and should not be performed. They mention that in their experiments they used defibrinated blood or crustic soda as an anticoagulant.

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36 Blundell, James 1790-1877

*Researches physiological and pathological with a view to the improvement of medical and surgical practice*

[London], 1825, opened at pl 2, p [143]  
Blundell's work "may be taken to mark the real beginning of the clinical application of blood transfusion" (Kevnes). The plate shows his "impellor", the instrument he used in transfusion, this work gives the records of his operations

37 Dieffenbach, Johann Friedrich 1790-1847

*Physiologische Untersuchungen über die Transfusion des Blutes*

In *Magazin für die gesammte Heilkunde* herausgegeben von Dr Johann Nep Rust Berlin, 1830, vol 30, p [3]

The experiments of this eminent surgeon led him to the conclusion that the blood of the same kind of animal should be used in transfusion, and that the blood of animals should not be injected in human veins.

38 Bischoff, Theodor Ludwig Wilhelm 1807-1882

*Beiträge zur lehre von dem Blute und der Transfusion desselben*

In *Archiv für Anatomie, Physiologie* herausgegeben von Dr Johannes Müller, Berlin, 1835, p 347

An account of the author's experiments with the injection of defibrinated blood to prevent coagulation.

39 Routh, Charles Henry Felix 1822-1909  
*Remarks, statistical and general, on transfusion*

In *Medical times*, 1849, vol 20, p 114  
The author records all the known cases of blood transfusion in an effort to show that "the operation is one of the safest major operations which may be practised in surgery." Case no 48 is an account of an operation of his own on a patient with cholera.

40 Brown-Sequard, Charles Edward 1817-1894

*Sur la persistance de la vie dans les membres atteints de la rigidité qu'on appelle cadaverique*

In *Comptes rendus hebdomadaires des séances de l'Académie des sciences* Paris, 1851, vol 32, p 855

The first of a number of articles on the experiments of this eminent physiologist. In this account he demonstrates that after the injection of blood into the arteries, muscles which have been attacked by rigor mortis, recover their voluntary movements. From later experiments he concludes that blood from the arteries given to animals by transfusion has a beneficial effect, whereas blood from the veins does not.

41 Louisiana State Medical Society

On the question of transfusion—being a report of a Committee Read March 16th, 1853 By N. B. Benedict

In *New Orleans medical and surgical journal*, 1853, vol. 10, opened at pp. 204-205

Description of an apparatus contrived by this Committee for facility in blood transfusion. The report contains a history of the subject as well as an account of Blundell's experiments. Benedict, a physician of New Orleans, joined the Society in 1852 and acted as Corresponding Secretary.

42 Higginson, Alfred 1808-1884

A report of seven cases of transfusion by blood, with a description of the instrument invented by the author.

In *Liverpool medico-chirurgical journal*, 1857, vol. 1, p. [102]

"An important modification was introduced into the technique of the operation in 1857, by Higginson, who applied the principle of a rubber syringe with ball-valves for transferring the blood from the receptacle into which it was drawn to the vein of the recipient" (Kevnes)

43 Richardson, (Sir) Benjamin Ward 1829-1896

The cause of the coagulation of the blood being the Astley Cooper prize essay for 1856

London, 1858, opened at p. 448

An account of experiments in which ammonia was employed in transfusion to prevent coagulation.

44 Martin, Eduard Arnold 1807-1875

Lehr die Transfusion bei Blutungen Neuentbundener

Berlin 1859, opened at pp. 18-19

These tables contain fifty-seven cases of hemorrhage at child-birth treated by blood transfusion in the years 1824-1857. Forty-five out of the fifty-seven operations were successful.

45 Blasius, Ernst 1802-1875

Statistik der Transfusion des Blutes

In *Monatsblatt f. medicinische Statistik*, (supp. to *Deutsche Klinik*) 1863, vol. 15, opened at pp. 80-81

Out of a total of 116 operations, in different countries, Blasius found that 56 had succeeded, 55 failed, and 5 were in doubt.

46 Panum, Peter Ludwig 1820-1885

Experimentelle Untersuchungen über die Transfusion, Transplantation oder Substitution des Blutes

In *Archiv für pathologische Anatomie und Physiologie von Rudolf Virchow*, Berlin, 1863, opened at p. 244

Panum lists the first experiments of transfusing defibrinated blood into human beings and gives an account of the earliest one, done in 1847, by Søren Eskildsen Larsen, b. 1802. Panum served as Dieffenbach's assistant at the Almindelig Hospital in Copenhagen, and is remembered for his work on the pathology of embolism. He favored the use of defibrinated blood in transfusion because it avoided the risk of embolism.

47 Kuhne, Willk 1837-1900

Verfahren bei Vergiftungen durch Kohlenoxyd

In *Centralblatt für die medicinischen Wissenschaften* Berlin, 1864, vol. 2, p. 134

Kuhne suggests the use of blood transfusion in the treatment of carbon monoxide poisoning.

48 Aveling, James Hobson 1828-1892

On immediate transfusion

In *Transactions of the Obstetrical Society of London*, 1865, vol. 6, opened at p. 133

A contemporary illustration of the direct transfusion of blood in England in the nineteenth century.

49 Hicks, John Braxton 1825-1897

On transfusion and new mode of management

In *British medical journal* 1865, vol.

- 2, p 151  
An account of the treatment of blood with phosphate of soda to retard coagulation during transfusion
- 50 Hueter, Karl 1838-1882  
Vorläufige Mittheilung betreffend die Transfusion von fieberfreiem Blut bei acuten, das Leben bedrohenden Wund- und Eiterfiebern  
In *Centralblatt für die medicinischen Wissenschaften*, 1869, vol 7, opened at p 390  
Hueter credits von Grafe with the introduction of arterial transfusion and goes on to describe his own method of injecting defibrinated blood from the vein of one to the artery of another. His success led him to conclude that it allowed the blood to reach the heart more slowly than other methods and prevented air embolisms. For a more detailed account of his experiments, see his article on the subject in *Archiv für klinische Chirurgie*, 1871, vol 12, p 1
- 51 Hooker, Ransom Spaford 1873—  
and Satterlee, Henry Snydam 1874—  
A special method for the transfusion of blood with the use of paraffin and hirudin  
In *Operative therapeutics*, edited by A B Johnson, 1916, vol 1, opened at p 339  
A description of the four general types of instruments for blood transfusion devised from about 1830 to 1880 with the names of those who invented them
- 52 Gesellius, Franz fl 1873  
Die Transfusion des Blutes  
St Petersburg & Leipzig, 1873, opened at p 19  
An illustration of the apparatus invented by this Russian physician to take blood from a healthy man for purposes of transfusion. In spite of his invention, Gesellius deplors the use of defibrinated human blood because of the lack of voluntary blood donors. He advocates the use of lamb's blood
- 53 Moncoq, D fl 1874  
Transfusion instantanée du sang  
Paris, 1874, opened at folding plate  
Illustrations of different types of instruments designed by the author for use in the transfusion of blood
- 54 Hasse, Oscar 1837-1898  
Die Lammblut-Transfusion beim Menschen  
St Petersburg and Leipzig, 1874  
Another advocate of the use of lamb's blood reports favorably on the outcome of his cases
- 55 Madge, Henry M fl 1859-ca 1890  
On transfusion of blood  
In *British medical journal*, 1874, vol 1, opened at p 44  
A report by the chairman of a committee of the Obstetrical Society of London appointed "to collect evidence, and to test, as far as possible, the real claims of transfusion to the confidence of the profession." Madge reports favorably upon transfusion but suggests 13 points calling for further inquiry
- 56 Ponfick, Emil 1844-1913  
Experimentelle Beiträge zur Lehre von der Transfusion  
In *Archiv für path anat*, 1875, vol 62, p [273]  
Ponfick's experiments bring him to the conclusion that the transfusion of blood between animals of a different kind are injurious. He notes that hematuria results from such a transfusion and suggests that hemoglobinuria is a more descriptive name
- 57 Landois, Leonard 1837-1902  
Die Transfusion des Blutes  
Leipzig, 1875, opened at p 184  
His important work shows the author's careful study of the changes which take place in the blood when transfused from one kind of animal to another. He points out the dissolution of the red blood corpuscles and the releasing of the hemoglobin
- 58 Thomas, Theodore Gaillard 1831-1903  
The intra-venous injection of milk as a substitute for the transfusion of blood  
In *New York medical journal*, 1878, vol 27, opened at p 165  
His New York physician gives an account of cases in which he injected milk into the veins, instead of blood. He

- predicts a brilliant future for "intravenous laceral injection"
- 59 Halsted, William Stewart 1852-1922  
Refusion in the treatment of carbonic oxide poisoning  
In *Annals of anatomy and surgery*  
Brooklyn, N Y, 1884, vol 9, p 7  
This eminent American surgeon advocates the use of centripetal arterial infusion in the treatment of carbon monoxide poisoning
- 60 von Ziemssen, Hugo Wilhelm, 1829-1902  
Ueber subcutane Blutinjektion und über eine neue Methode der intravenösen Transfusion  
In *Verhandlungen des (11) Congresses für innere Medizin*, 1892, opened at pp 168-169  
This eminent physician's first method was the injection of blood subcutaneously His later method was the withdrawal of blood into a syringe in order to inject it into the vein of the patient He advised the use of three syringes and as many assistants
- 61 Murphv, John Benjamin 1857-1916  
Resection of arteries and veins injured in continuity—end-to-end suture—experimental and clinical research  
In *Medical record*, 1897, vol 51, opened at pp 74-75  
Illustrations of end-to-end suture of veins and arteries which proved a great stimulus to surgery of the blood vessels
- BLOOD TRANSFUSION IN THE TWENTIETH CENTURY
- 62 Shattock, Samuel George 1852-1924  
Chromocyte clumping in acute pneumonia and certain other diseases, and the significance of the buffy coat in the shed blood  
In *Journal of pathology and bacteriology*, 1900, vol 6, opened at p 306  
An account of his discovery that the serum of a horse agglutinates the corpuscles of a human being
- 63 Landsteiner, Karl 1868—  
Ueber Agglutinationserscheinungen normalen menschlichen Blutes  
In *Wiener klinische Wochenschrift*, 1901, vol 14, p 1132  
The author's account of his experiments showing that human blood contains isoagglutinins, capable of agglutinating other human red blood corpuscles He divides human blood in three groups Shattock's work was done independently
- 64 Decastello-Rechtwehr, Alfred 1872—  
& Sturli, Adriano  
Ueber die Isoagglutinine in Serum gesunder und kranker Menschen  
In *Muenchener medizinische Wochenschrift*, 1902, vol 49, opened at pp 1092-1093  
An account of the experiments which showed the discovery of the fourth and rarest blood group
- 65 Carrel, Alexis 1873—  
La technique opératoire des anastomoses vasculaires et la transplantation des viscères  
In *Lyon medical*, 1902, vol 98, opened at pp 862-863  
The first of Carrel's papers on end-to-end anastomosis of blood-vessels, which revolutionized the surgery of the vascular system
- 66 Jinsky, Jan  
Haematologische studie u psychotiku  
In *Sborník klinický*, 1907, vol 8, opened at p 132  
A resume of the first account of the classification of human blood into four groups
- 67 Hektoen, Ludwig 1863-  
Isoagglutination of human corpuscles  
In *Journal of infectious diseases*, 1907, vol 4, p 297  
An account of experiments which led the author to point out the dangers of homologous blood transfusion arising from the common occurrence of isoagglutinins in human serum This danger can be avoided by the selection of a donor whose corpuscles are not agglutinated by the serum of the recipient, and whose serum does not agglutinate the corpuscles of the latter that is to say, donor and recipient should belong to the same group and preferably to Group I or II
- 68 Crile George Washington 1864-  
The technique of direct transfusion of blood

- In *Annals of surgery*, 1907, vol 46, p 329  
A description of Crile's method of direct blood transfusion which eliminated many dangers and was 'the first to render the operation of transfusion a comparatively popular one' (Keynes)
- 69 Lambert, Samuel Waldron 1859-  
*Melæna neonatorum*, with report of a case cured by transfusion  
Repr *Medical record*, 1908, vol 73, p [885]  
An account of the cure of a case of *melæna neonatorum* by means of direct blood transfusion by end-to-end anastomosis, performed by Dr Carrel
- 70 Ottenberg, Reuben 1882-  
Transfusion and arterial anastomosis  
In *Annals of surgery* 1908, vol 47, opened at p 505  
The author's experiments led him to the conclusion that transfusion would be made more safe if it is determined beforehand whether hemolysis is likely to occur when any two given bloods are mixed
- 71 Elsberg, Charles Albert 1871-  
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In *Journal of the American medical association*, vol 52, 1909, opened at p 888  
Description of a simplification of the Crile cannula
- 72 Hartwell, John Augustus 1869-  
A simple method of blood transfusion without cannula  
In *Journal of the American medical association* 1909, vol 52, p 297  
An account of experiments in which the end of the artery is slipped directly into the end of the vein
- 73 Brewer, George Emerson 1861- & Leggett, Noel Bleecker  
Direct blood transfusion by means of paraffin coated glass tubes  
In *Surgery gynecology and obstetrics* 1909, vol 9, p 293  
The authors propose a new method to facilitate direct blood transfusion
- 74 Crile, George Washington 1864-  
Hemorrhage and transfusion  
N Y and London, 1909, opened at p 292  
Illustration of the stages of end-to-end anastomosis of two blood vessels by the cannula method
- 75 Moss, William Lorenzo 1876-  
Studies on isoagglutinins and isohemolysins  
In *Bulletin of the Johns Hopkins hospital*, 1910, vol 21, opened at p 66  
The Moss classification of the blood groups This was done independently of Jansky's work, and the use of both systems of classification caused confusion and actual danger
- 76 Curtis, Arthur Hale 1881- & David, Vernon Cyrenius 1882-  
Transfusion of blood by a new method, allowing accurate measurement  
In *Journal of the American medical association*, 1911, vol 56, p 35  
Description of transfusion with a syringe and a two-armed cannula which has been coated with paraffin on the inside
- 77 Kimpton, Arthur Ronald 1881- & Brown, James Howard 1884-  
A new and simple method of transfusion  
Repr *Journal of the American medical association*, 1913, vol 61, pp 117-118  
An account of indirect transfusion by means of a paraffin coated vessel
- 78 Lindeman, Edward 1879-1919  
Simple syringe transfusion with special cannulas  
In *American journal of diseases of children*, 1913, vol 6, p 28  
This revival of Ziemssen's method employs two sets of cannulas, two tourniquets and twelve syringes The account was read at The New York Academy of Medicine on April 10th, 1913
- 79 Abel, John Jacob 1857- , Rountree, Leonard George 1883- & Turner, Benjamin Bernard  
Plasma removal with return of corpuscles (plasmaphæresis)  
In *Journal of pharmacology and experimental therapeutics*, 1913-1914, vol 5, opened at p 628  
An early experiment using hirudin to prevent coagulation
- 80 Hustin, Albert 1882-

- Principe d'une nouvelle methode de transfusion muqueuse  
In *Journal medical de Bruxelles*, 1914, vol 19, opened at p 437  
This Belgium physician advocated the use of sodium citrate as an anticoagulant In one case he employed a citrate solution mixed with glucose
- 81 Agote, Luis 1868-  
Nuevo procedimiento para la transfusion del sangre  
In *Anales del Instituto modelo de clinica medica*, 1915, vol 1, opened at p 27  
An important account of transfusion in which sodium citrate was used to prevent coagulation He employed one gram of a 25 per cent citrate solution to a hundred grams of blood
- 82 Weil, Richard 1876-1917  
Sodium citrate in the transfusion of blood  
Repr *Journal of the American medical association*, 1915, vol 64, p 425  
An account of Weils experiments with sodium citrate
- 83 Lewisoohn, Richard 1875-  
A new and greatly simplified method of blood transfusion  
In *Medical record*, 1915, vol 87, p 141  
An account of the experiments of this American physician who helped to introduce in this country the use of sodium citrate as an anticoagulant He reached the conclusion that the amount of sodium necessary is only 0.2 per cent His work was done independently of Hustin, Agote and Weil
- 84 Linger, Lester Jarecki 1888-  
A new method of syringe transfusion  
In *Journal of the American medical association* 1915, vol 64, p 582  
A modification of the syringe method in which a continuous injection of salt solution is made to prevent clotting An ether spray keeps the syringe cool (See his article in this same journal for September 18 1915)
- 85 Rous, Francis Peyton 1879-  
& Lurner, Joseph Richard 1889-  
The preservation of living red blood cells in vitro  
In *Journal of experimental medicine*, 1916, vol 23, opened at pp 246-247  
This important work suggests the addition of glucose and sodium citrate for the preservation of blood cells
- 86 Robertson, Oswald Hope 1886-  
A method of citrated blood transfusion  
In *British medical journal*, 1918, vol 1, p 477  
It was largely through Robertson's work that the citrate method of transfusion was introduced to the armies abroad during the World War
- 87 Isohemagglutination Recommendation that the Jansky classification be adopted for universal use  
In *Journal of the American medical association*, 1921, vol 76, p 130  
The confusion arising from the fact that both the Moss and Jansky classifications were in use at the same time, led to the appointment of a special committee to consider the matter The members of the committee, representing the American Association of Immunologists, the Society of American Bacteriologists and the Association of Pathologists and Bacteriologists, unanimously recommended that the Jansky classification be adopted for universal use, solely on the basis of its priority
- 88 Landsteiner, Karl 1868-  
The human blood groups  
In *Newer knowledge of bacteriology and immunology* (Jordan and Falk), [1928], p 892  
In spite of the recommendation that the Jansky classification should be used universally, many institutions continued to use the Moss classification Landsteiner suggests that the groups be designated by the letters O, A, B and AB, a classification later adopted as the international classification

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  - 19 Snethlage, Rudolf Abraham Iduard \*Bydrage tot de geschiedenis der Transfusio sanguinis Amsterdam, 1876
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\* Inaugural dissertation

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\* Prepared by Frank Place, Chief Reference Librarian, New York Academy of Medicine

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BULLETIN OF  
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OCTOBER 1939

PROTEINS AS CHEMICAL SUBSTANCES  
AND AS BIOLOGICAL COMPONENTS

EDWIN J COHN

*Harvey Lecture, January 19, 1939*

THE importance of the diverse class of molecules that we know as proteins has in recent years become ever more apparent. Proteins were regarded as chemical substances even a century ago. Thus in 1838, Mulder reported elementary analyses of various proteins, including egg and serum albumins, and estimated minimal molecular weights of over 50,000 on the basis of their sulfur and phosphorus content<sup>1</sup>.

The sulfur and phosphorus analyses of Mulder were in error, and so were the atomic weights that he employed. But the concept of proteins as chemical substances is implicit in his calculations.

Three years later<sup>†</sup> than the number containing Mulder's analyses there appeared a discussion in Liebig's *Annalen* of a communication from the French scientist Denis to Liebig in which is described the separation of blood proteins into those soluble in water, and those which were only soluble in salt solutions, that is, into albumins and globulins<sup>2</sup>. A century ago, therefore, there was a beginning not only of the characterization of proteins as chemical substances, but the fractionation of tissues into their

<sup>†</sup> In the same volume is a communication of Dr. Bence Jones<sup>3</sup> on the nitrogen containing foodstuffs of the plant world, on the albumins of the brain, and of the egg yolk, reporting analyses carried out in part with Liebig in the Chemical Laboratory in Giessen.



TABLE I\*

	Fibrin		Albumin	
			v Eiern	v Serum
Kohlenstoff	54,56	—	54,48	54,84
Wasserstoff	6,90	—	7,01	7,09
Stickstoff	15,72	—	15,70	15,83
Sauerstoff	22,13	—	22,00	21,23
Phosphor	0,33	—	0,43	0,33
Schwefel	0,36	—	0,38	0,68

Auf die kleinere Zahl der Atome von Schwefel und Phosphor berechnet, erhält man:

	Fibrin u Atome		Albumin v Eiern in 100 Th		Albumin v Serum Atome		in 100 Th
Kohlenstoff	400	—	54,90	—	400	—	54,70
Wasserstoff	620	—	6,95	—	620	—	6,92
Stickstoff	100	—	15,89	—	100	—	15,84
Sauerstoff	120	—	21,55	—	120	—	21,47
Phosphor	1	—	0,35	—	1	—	0,35
Schwefel	1	—	0,36	—	2	—	0,72
Atomgewicht = 55692,61		—			= 55893,78		

### protein components

In the intervening century more and more proteins have been isolated from biological systems, purified and characterized by ever improving methods. The reserve proteins of the seeds of plants were presumably the first to be observed in a crystalline state. Until recently the proteins most investigated were the seed globulins, the proteins of the body fluids, such as hemoglobin, the protein of the blood corpuscle which carries oxygen to the tissues, the albumins of serum and of egg white, the casein of milk, the fibrinogen of plasma responsible for the clotting of the blood, the serum globulins, bearers of immunity, and the globulin of muscle, myosin, concerned with muscular contraction. The latter protein has been repeatedly investigated from many points of view and may be said to represent the transition to the study of tissue proteins, that is, to those molecules to which we now look as elements of morphological structure in the body.

That certain hormones and enzymes are protein in nature has only recently become apparent. The iodine-containing hormone of the thy-

\* Reproduced from Mulder.<sup>1</sup>

roid gland, the active principle of which is thyroxin or some closely related configuration, is thyroglobulin. In thyroglobulin as in hemoglobin, the active configuration is a prosthetic group containing an element—iodine in the one, iron in the other—not found in most proteins.

Another hormone which has been proven to be protein in nature is the insulin effective in the treatment of diabetes, discovered by Banting and crystallized by Abel. The large number of studies in different laboratories on insulin have thus far failed to reveal, as du Vigneaud has pointed out,<sup>4</sup> any prosthetic group and thus demonstrated that a pure protein may serve as a hormone.

It is over a decade since Sumner<sup>5</sup> first crystallized an enzyme, the urea splitting urease, and found it to be a protein. Northrop and his colleagues' crystallization of pepsin, pepsinogen, trypsin, trypsinogen, and chymotrypsin,<sup>6</sup> all digestive enzymes, and Sumner's of catalase<sup>7</sup> followed, and it has become apparent from much of Northrop's<sup>6</sup> and of Bergmann's work<sup>7,8</sup> that the specificity of enzymes depends upon the chemical structure of the protein molecule.

The vitamins were discovered as a consequence of investigations of the nutritional requirements of the body. Therapy consisted in adding vitamins to the diet, but their physiological function and morphological locus remained unknown. Recently it has been demonstrated that riboflavin which is part of the vitamin B<sub>2</sub> complex is the prosthetic group<sup>9</sup> of the yellow enzyme of Warburg<sup>10</sup> and that the carotenoids, which are known as vitamin A<sub>1</sub> and A<sub>2</sub> are the prosthetic group<sup>11</sup> of visual purple, a protein with a molecular weight of about 250,000.<sup>12</sup>

The bearers of immunity have long been associated with the globulin fractions of the serum. In how far the very great specificity of immune reactions inheres in these, in how far in the specific polysaccharides<sup>13</sup> with which antigens are associated, is still being investigated.

One must now add to the proteins of importance in physiology, pharmacology, morphology and pathology, at least certain of the viruses hitherto the concern of bacteriology. The virus sizes were known as the result of a series of ultrafiltration studies by Zinsser,<sup>14</sup> Bechhold,<sup>15</sup> Elford,<sup>16</sup> and others,<sup>17</sup> but it remained for Stanley<sup>18,19</sup> to isolate the virus of tobacco mosaic disease, and demonstrate that it was protein in nature. The huge size of tobacco mosaic virus has been deduced from ultracentrifugal studies<sup>20</sup> and its long asymmetrical shape has been investigated by the method of double refraction of flow.<sup>21,22</sup> Like the myosin

of skeletal muscle,<sup>23</sup> tobacco mosaic virus appears to have a length greater than 5,000 Angstroms, a value which may be contrasted with a diameter of 15 Angstroms of the carbon atom, and 44 Angstroms for proteins of the molecular weights of pepsin, insulin and lactoglobulin provided they be considered spherical. Not all of the proteins of body fluids are, however, to be regarded as spherical, and not all viruses as elongated. Among the former fibrinogen, the protein involved in the clotting of blood, is elongated and among the latter the newly crystallized Bushy Stunt virus of the tomato<sup>24</sup> is nearly spherical.<sup>25</sup>

The diversity of the functions subserved by protein molecules is not greater than the diversity in their sizes, shapes, and stereochemical configurations. Obviously some of the methods that must be employed for the study of these protein molecules were not envisioned by earlier chemical and biochemical investigators. New methods have been developed as the new molecules were discovered and the numbers of them that have been and are being perfected is increasingly gratifying.

#### THE POLAR AND NON-POLAR GROUPS OF PROTEINS

Despite the diversity in the form and function of proteins, the number of well recognized chemical configurations which constitute the side chains of the amino acids and therefore of the proteins is by no means large. Without considering here either the methods that are available for the estimation of the amino acid composition of proteins, or the manner in which the peptide chain is ordered in the protein, one may consider the nature of the various configurations which constitute the reactive groups of proteins. In Table II molecular weights are given for a few proteins whose amino acid compositions have been partially apprehended. Only the analytical procedures for sulfur and sulfide sulfur, for cystine and methionine, and for tryptophane and tyrosine have been employed in estimating their minimal molecular weights which have elsewhere been compared<sup>26,27</sup> with those deduced from the osmotic pressure measurements of Sorensen, Adair and Burk, and the beautiful ultracentrifugal studies of Svedberg and his coworkers.<sup>28</sup> The number of sulfhydryl and methionyl, of indole and phenolic hydroxyl groups per mole were then computed. The estimates of imidazol groups derived from histidine analysis and of guanidine groups derived from arginine analysis may be considered fairly accurate. But the estimates of  $-\text{NH}_3^+$  equivalent to  $\epsilon$ -amino groups, may well be low since they are based upon

determinations of lysine, often estimated by difference, and besides do not include the hydroxylysine whose isolation from protein has recently been reported<sup>29</sup>

The guanidine group is the most basic of which proteins are possessed, and the properties of the protamines must in large part be considered to depend upon this configuration. The  $\epsilon$ -amino group dissociates with a strength which varies widely with its position in the molecule, but is in any case also strongly basic, whereas the imidazole group present in such large amounts in hemoglobin dissociates at more nearly neutral reactions. These three configurations alone bear positive charges in acid solutions, are responsible for the cationic properties of the proteins, and are present in such amounts as quantitatively to account for their acid combining capacities<sup>30 31</sup>

The dicarboxylic acids yield free carboxyl groups when bound in peptide linkage. However, a portion of the dicarboxylic acids, equivalent to that revealed by determinations of ammonia, are considered to be present in the native protein as amides of the type of asparagine and glutamine. The estimate of carboxyl groups, the only acid groups (if we omit from consideration those of phosphoric acid) which dissociate in relatively acid solution and bear negative charges at neutral reactions must be considered less satisfactory, not only because of the analytical procedures that have thus far been employed, but because the result is a difference between various analytical procedures.

Although only carboxyl groups presumably bear negative charges at acid and neutral reactions, the phenolic hydroxyl group of tyrosine and the sulfhydryl group of cysteine yield negatively charged groups and may therefore be considered to add to the anionic valence of proteins, in so far as these configurations exist<sup>31 32 33 34 35</sup> in the native molecule. In the case of many proteins there is no evidence of free SH groups in the native state, but in certain others, such as myosin,<sup>23 33</sup> sulfhydryl groups appear to be free, and these should dissociate at roughly the same alkalinities as free phenolic hydroxyl groups.

The simplest of the amino acids, glycine, contributes neither anionic nor cationic properties to the protein in which it is held in peptide linkage. Nor does it contribute a side chain terminating in a polar or non-polar group. Absence of side chains permits glycine peptides to pack closely in the crystal lattice and presumably is related to their low solubilities. Residues of glycine situated between those of other amino acids

cannot pack equally closely, but rather may be thought of as creating cavities on the surface of the molecule

Of the side chains which do not lead to ionic configurations the amide groups combined with dicarboxylic acids, the hydroxyl groups of serine, threonine, hydroxyproline, and presumably other hydroxy amino acids, must be considered very polar \*. On the other hand, the benzene ring of phenylalanine, and those parts of the pyrrolidine ring of proline that extend from the peptide chain must be considered non-polar

Aside from its polar nature, the hydroxyl group has significance for the chemistry of the proteins because of its close relation to the solvent water, because of its capacity to enter into ester linkage with acids, being the point of attachment of phosphorus at least in certain phosphoproteins, and because of the possible role, not considered here, of the hydroxyl bond for internal protein structure

Whereas the hydroxyl groups of aliphatic amino acids and of hydroxyproline, the sulfur of methionine and the nitrogen of the indole group must be considered polar, the configurations of which they are a part reflect also their non-polar groups. Thus tryptophane and methionine behave in many respects like leucine

The number of  $\text{CH}_2$  groups vary in the aliphatic series from glycine to leucine and this will affect interactions with polar and non-polar solvent and solute molecules in various ways <sup>36, 37</sup> Moreover, the spatial arrangements of amino acid residues of various side chain lengths must have a determining influence on the distance of closest approach of protein molecules both with ions, dipolar ions, and uncharged molecules

It is of interest to note the differences in the free groups of different proteins (Table II) and to point out the importance that must be attached to the improvement of analytical procedures upon which our notions of the fine structure of the proteins must ultimately rest. Many

\* As judged by the solubility ratio in ethanol and water  $\log N_1/N_0$  (see Table III) asparagine, glutamine, as well as aspartic and glutamic acids and all the hydroxy acids studied thus far are nearly as polar as glycine and all more polar than alanine. Thus the values of  $\log N_1/N_0$  for glycine, asparagine, glutamine, aspartic and glutamic acids, serine, threonine and hydroxyproline are —3.391, —3.402, —3.466, —2.999, —2.992, —3.362, —3.070, —2.893

<sup>†</sup> "the peptides of glycine may be considered as simple cylinders of alternating segments of radii 2.61 Å in the neighborhood of the  $\text{CH}_2$  group and 2.12 Å in the neighborhood of the amide group. The average radius on this basis would be 2.32 Å, which is one half the distance of nearest approach of parallel polypeptide chains."

"Substitution of an alanine for a glycyl residue in the peptide chain may be considered as adding a branch extending 1.26 Å from the cylinder. Valine would extend the branch to 2.52 Å, norvaline or leucine to 3.78 Å and norleucine to 5.04 Å." <sup>38</sup> Astbury gives a side spacing of the order of 4.1' to 5 Å in most of the x-ray photographs of proteins <sup>39</sup> (p. 199)

"In terms of the dimension of the  $\text{CH}_2$  and  $\text{CONH}$  groups the packing of peptide chains in the two planes should be given by 4.64 (i.e.,  $2 \times 2.32$ ) and 9.68 (i.e.,  $2 \times 4.84$ ) Å the amino acids of the protein having hydrocarbon chains on the average of the length of valine. The presence of amino acids with longer hydrocarbon chains would of course still further increase the distance in this plane between parallel polypeptide chains" <sup>38</sup> (p. 95)

TABLE II

NATURE AND NUMBER OF POLAR AND NON-POLAR  
SIDE CHAIN GROUPS OF CERTAIN PROTEINS

SUBSTANCE	MOLECULAR WEIGHT	CATIONIC GROUPS			ANIONIC GROUPS			NON IONIC POLAR GROUPS				NON POLAR GROUPS			
		Guanidine	Ammonium	Imidazole	Carboxyl	Phenolic hydroxyl	Sulfhydryl or $\frac{1}{2}$ (S S)	Amide	Hydroxyl	Methionyl	Indole	Paraffin	Benzene	Pyrrolidine	Glycine
		Number of Groups													
Glycine	75		1		1										
Cystine	240		2		2		2								
Salmin	5,600	24			1				4					6	
Egg Albumin	35,000	12	12	4	28	8	6	27		12	2	45	12	12	
Insulin	35,000	6	6	18	36	24	36	36				81	+	+	
Zein	39,000	4	0	2	10	12	3	84	6	6		122	18	30	
Gladin	42,000	9	2	9	18	8	8	128	1	6	2	43	6	48	0
Hemoglobin	66,700	16	38	33		12	4		8	4	4	180	18	12	
Serum albumin	73,000	20	66	16	*	18	36	56	4		2	134	14	6	
Casein	96,000	21	42	16	146	+	3	90	6	21	8	156	24	72	6
Edestin	309,000	288	72	42	228	78	36	414	58	48	24	616	60	112	

\* The values for the sum of the dicarboxylic acids thus far available are even smaller than demanded by the ammonia analysis. The high base combining capacity of serum albumin suggests the desirability of new studies of the dicarboxylic acids of the serum albumins.  
† Too discrepant results to be considered

In constructing this table the following assumptions have been made relating the groups to the amino acids found on hydrolysis

- Guanidine = Arginine
- Ammonium = Lysine
- Imidazole = Histidine
- Carboxyl = Aspartic + glutamic +  $\beta$  hydroxyglutamic acid — ammonia
- Phenolic hydroxyl = Tyrosine
- Sulfhydryl or  $\frac{1}{2}$  (S S) =  $2 \times$  Cystine or alkali labile sulfur if in excess of cysteine sulfur
- Amide = Ammonia
- Hydroxyl = Serine + threonine + hydroxyproline. The numbers of the reported residues of hydroxyglutamic acid are 3 for egg albumin 6 for zein 20 for gladin and 64 for casein and not included here but have been counted as carboxyl groups
- Methionyl = Methionine or total sulfur — alkali labile sulfur
- Indole = Tryptophane
- Paraffin = Alanine + valine + leucine + norleucine. Threonine and methionine are not included since certain of their non polar groups are situated between polar groups. The total number of  $\text{CH}_2$  groups in paraffin side chains (alanine + serine) + 2 threonine + 3 (valine + methionine) + 4 (leucine + norleucine) is for present estimates on these proteins 181 324 378 152 648 474 576 2246 respectively for egg albumin insulin zein, gladin hemoglobin serum albumin casein and edestin
- Benzene = Phenylalanine. In tyrosine the benzene rings are situated between polar groups. The number of such benzene rings is given by the number of phenolic hydroxyl groups
- Pyrrolidine = Proline. In hydroxyproline the non polar groups are situated between the hydroxyl groups and the peptide chain. The numbers of these included in the number of hydroxyl groups are 2 for zein 4 for hemoglobin 2 for casein and 48 for edestin. The hydroxyl minus the hydroxyproline groups yield of course serine plus threonine

proteins appear to have molecular weights ranging from 34,000 to 42,000. The analyses on the basis of which their percentile compositions have been determined have been,<sup>8,26,40</sup> and will be, discussed elsewhere. Although it must be remembered that in many cases the number of groups of any kind may at this time only be estimates, since the analytical evidence regarding many of these residues is by no means satisfactory, there is none the less an advantage in considering the differences in protein molecules which emerge from the analyses at present available.

Zein and gliadin among those of roughly the same molecular weight are classified as prolamines. That is to say, they are insoluble in water, but soluble in alcohol-water mixtures. Their compositions are known to over 90 per cent, and so it would appear to be significant that they contain but very few basic amino acids and very few free carboxyl groups, but consist predominantly of glutamine and asparagine, of proline and of mono-amino monocarboxylic acids with paraffin side chains. Even certain differences between zein and gliadin may be worth noting. Thus the former is poorer in amide and pyrrolidine groups, whereas the latter is poorer in the number of non-polar  $\text{CH}_2$  groups in paraffin side chains.

As compared with the six cationic and eight or ten carboxylic groups of zein, and the eighteen cationic and eighteen free carboxylic groups of gliadin, egg albumin has approximately twenty-eight cationic and an equal number of free carboxylic groups and is extremely soluble in water, being, therefore, classified as an albumin. The protein of roughly the same molecular weight, crystallized some years since from the albumin fraction of milk by Palmer,<sup>41</sup> has a solubility of approximately 0.8 gram per liter in water at  $25^\circ \text{C}$ , but is relatively soluble in salt solutions and has therefore been called lactoglobulin. Although we already know a great deal about this protein as a result of physical-chemical studies,<sup>42</sup> analytical studies regarding its amino acid composition remain inadequate.

Two of the other proteins of this size have well known physiological functions: pepsin is an enzyme, insulin a hormone. Pepsin is very poor in basic amino acids, rich in free carboxyl groups and has a very acid isoelectric point. It is also richer in tyrosine than the other proteins thus far considered, though not richer than insulin. Perhaps the outstanding characteristic of the latter protein, however, is the large number of cystine residues that it contains rather than its electrically charged groups, which would not appear on the basis of existing analyses to be

very different from those of other proteins. Pepsin may be classified as a globulin, since it is soluble in salt solutions but not in distilled water. Certainly there are differences in the composition of these proteins of nearly the same size and shape, but certainly also these do not yet suffice to allow us to predict behavior—especially physiological behavior.

The evidence thus far available suggests that the molecular weight in dilute aqueous salt solution of hemoglobin, of casein and of edestin are of the sizes indicated. These molecular weights are many times the minimal molecular weights calculated on the basis of composition, and it has been reported that the molecular weights of these proteins in concentrated urea solutions and also under certain other conditions are far smaller. The number of reactive groups of each kind in these proteins may most readily be compared with those of molecular weights from 34,000 to 42,000 by dividing the results for hemoglobin by two, for casein by three, and for edestin by from six to eight. Among other differences it should be noted that edestin is far richer in guanidine, and hemoglobin in the imidazole group. The imidazole group of the latter has been demonstrated to be in such a relation to the prosthetic iron containing group that its state influences the combination of the protein with oxygen.<sup>43 44 45</sup>

Physiological behavior may often depend upon a very small fragment of the molecule, the groups of which are arranged in a special configuration. In the case of hemoglobin and of cytochrome, of the hemocyanins, of the yellow enzymes, and of certain other proteins the reactive group may be considered as prosthetic, that is, as not being derived from amino acids. In the case of insulin, however, as we have seen, investigation has thus far revealed no components of the molecule other than the normally occurring amino acids, and the specificity of physiological behavior of this molecule,<sup>4</sup> as of many enzymes,<sup>6 7</sup> would thus appear to depend merely upon the arrangement in space of charged and uncharged, polar and non-polar side chains.

#### INFLUENCE OF POLAR AND NON-POLAR GROUPS UPON SOLUBILITY IN ORGANIC SOLVENTS

Certain correlations can be made between proteins that are rich in cationic groups and in acid combining capacity, between those that are rich in anionic groups and in base combining capacity, and that are poor in ionic groups, and therefore in amphoteric properties. Those among



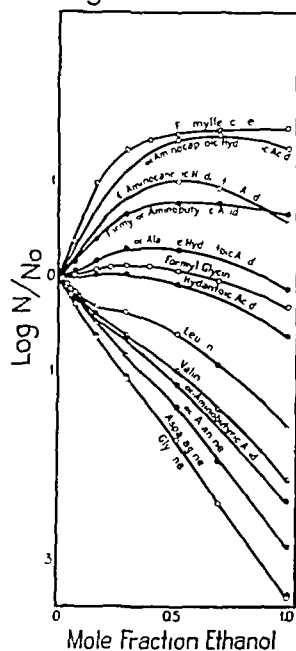
Influence of  
Organic Molecules

Fig 1a

Influence of Ions

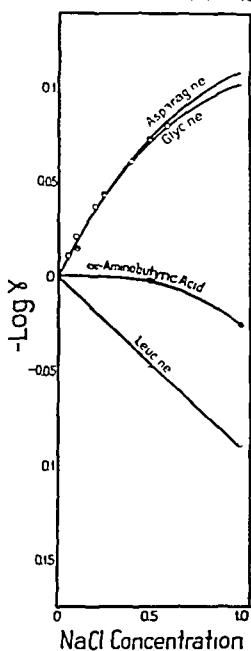


Fig 1b

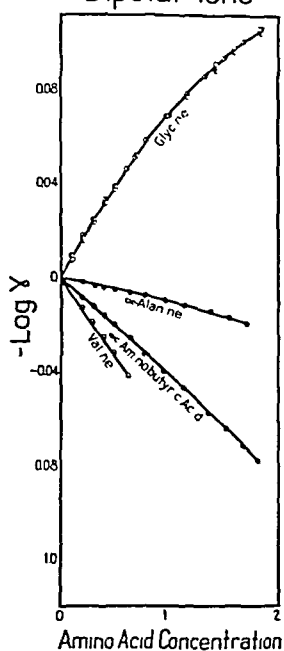
Influence of  
Dipolar Ions

Fig 1c

the latter rich in pyrrolidine and paraffin groups appear also to be more soluble in ethanol-water mixtures than in aqueous solutions and this has been the method for their isolation and the basis for their classification. It has been possible to develop a firm quantitative foundation for these generalizations by studying molecules of known structure containing the various groups of which proteins are possessed.

Glycine is the most soluble in water of the mono-amino mono-carboxylic, aliphatic  $\alpha$ -amino acids. The additional  $\text{CH}_2$  group of alanine renders it less soluble in water. Valine with 3  $\text{CH}_2$  groups in its side chain is still less soluble,<sup>46</sup> and the solubility of leucine with 4 such  $\text{CH}_2$  groups is 0.0744 mole per liter as contrasted with 2.886 moles per liter for glycine at  $25^\circ \text{C}$ . These amino acids are all far less soluble in alcohol-water mixtures than in water, but the effect of alcohol in diminishing solubility is smaller the larger the number of  $\text{CH}_2$  groups of which the  $\alpha$ -amino acid is possessed. This is illustrated in Fig 1a in which the logarithm of the solubility in any given solvent,  $N$ , divided by that in water,  $N_0$ , is plotted as ordinate and the mole fraction ethanol in the system as abscissa. That the smaller effect of ethanol in diminishing solu-

bility the longer the paraffin side chain depends upon the dipolar ionic nature of the neutral amino acids has been demonstrated by their comparison with certain of their derivatives that have been purified or synthesized by my colleague, T L Meekin

Curves describing the behavior in ethanol-water mixtures of the formyl derivatives of the amino acids and their hydantoic acids,<sup>47</sup> also form a family, though their shape is quite different from that of the amino acids from which they are derived Whereas small amounts of alcohol diminish the solubility of  $\alpha$ -amino acids, they increase the solubility of their derivatives which are no longer dipolar ions This is particularly marked with formylleucine and  $\alpha$ -aminocaproic hydantoic acid The additional  $\text{CH}_2$  groups of these molecules as compared with hydantoic acid are reflected by increased solubility in systems rich in ethanol The isomeric  $\alpha$ -aminocaproic hydantoic acid, in which the  $\text{CH}_2$  groups lie between polar groups behaves far more like the formyl derivative of  $\alpha$ -aminobutyric acid<sup>47</sup>, that is to say, like a molecule with two less  $\text{CH}_2$  groups Its solubility in 80 per cent ethanol is approximately tenfold that in water and threefold that in ethanol, a type of behavior characteristic of the prolamines, zein and gliadin

The influence of each  $\text{CH}_2$  group in the transfer from water to ethanol would, however, appear to be the same for the  $\alpha$ -amino acids or for their derivatives This has previously been demonstrated<sup>46</sup> on the basis of data such as that in Table III by subtracting  $\log N_A/N_0$  (where  $N_A$  is the solubility in mole fraction in ethanol) of glycine from alanine and from  $\alpha$ -aminobutyric acid The differences per  $\text{CH}_2$  group are the same, not only for this comparison but for that of the other amino acids of the same family that have been adequately studied in this way, as well as for derivatives of the amino acids and for isomers of the amino acids, such as the  $\alpha$  hydroxyamides, glycolamide and lactamide, which have the same composition though different structures than the amino acids Moreover, expressed in these terms the effect is always positive and may tentatively be put equal to 0.5 Differently stated *each  $\text{CH}_2$  group in side chains terminating in a methyl group may be thought of as increasing solubility in ethanol relative to that in water threefold for each  $\text{CH}_2$  group*

The non-polar  $\text{CH}_2$  group does not have this effect when placed between polar groups<sup>47</sup> In the peptide chain  $\text{CH}_2$  groups alternate with  $\text{CONH}$  groups and the element  $\text{CH}_2\text{CONH}$  may therefore be con-

sidered as the repeating pattern in the protein and as having a length in the stretched condition of 3.5 Å as revealed by x-ray studies of the fibrous proteins<sup>39,48</sup>

The influence of the configuration  $\text{CH}_2\text{CONH}$  is opposite in sign to that of the  $\text{CH}_2$  group as is demonstrated by the studies of three series of compounds in Table III. This configuration, which constitutes the backbone of the protein molecule, as well as certain protein side chains, must therefore be considered strongly polar in nature.<sup>49</sup>

The hydroxyl group must also be considered polar, indeed it is because of this group that the glycerols, alcohols, and water are to be regarded as polar solvents, water being the most polar since it has no  $\text{CH}_2$  group.

The influence of the hydroxyl group in proteins on the transfer from water to ethanol is estimated in Table III from a comparison of amides and hydroxyamides, of serine and alanine and of threonine and  $\alpha$ -amino-n-butyric acid.<sup>49</sup> The comparisons of hydroxyproline and proline and of tyrosine and phenylalanine are omitted, since they include the effect on non-polar carbon rings of their position between polar groups.

The sulfur of methionine is between non-polar groups, and comparison of this molecule with one of the same composition save for the sulfur suggests that the latter diminishes the influence of the paraffin side chain by an amount approximately equal to one  $\text{CH}_2$  group. Comparison of phenylalanine with alanine however demonstrates that *the effect of the non-polar benzene ring is of the same sign as the effect of the  $\text{CH}_2$  group, but opposite in sign to the  $\text{CH}_2\text{CONH}$  and OH groups*

Far greater than any of these is the influence of dipolar ionic structure. The demonstration in 1923 by Bjerrum<sup>50</sup> that amino acids were to be regarded as zwitterions or dipolar ions rendered it possible to understand the very strongly polar nature not only of amino acids, peptides and proteins, but their far higher solubility in water than in non-polar solvents. The amino acids are compared with certain of their derivatives in Fig. 1 and in Table III. The change in  $\log N_A/N_0$  may be taken as close to -2.7, whether amino acids and peptides are compared with hydantoic acids or with  $\alpha$ -hydroxy-amides. *The influence of dipolar ionic structure upon this transfer is therefore at least four times as great as that of an hydroxyl group or of the  $\text{CH}_2\text{CONH}$  configuration.* Although the backbone of the protein may thus be conceived of as consisting of alternating polar and non-polar groups, and although many of

TABLE III

INFLUENCE OF STRUCTURE ON SOLUBILITY IN WATER AND ETHANOL AT 25°

Substance	LOG $N_A/N_0$	LOG $N_A/N_0$	$\left( \frac{\Delta \log N_A/N_0}{n} \right)$
Influence of CH <sub>2</sub> group			
Glycine-alanine	-3 391	-2 856	+0 54
Glycine- <i>a</i> -aminobutyric acid	-3 391	-2 375	+0 50
Glycine- <i>a</i> -aminocaproic acid	-3 391	-1 414	+0 49
Valine-leucine	-2 158	-1 622	+0 54
Hydantoic- <i>a</i> -alanine hydantoic acid	-0 630	-0 137	+0 49
Hydantoic- <i>a</i> -aminocaproic hydantoic acid	-0 630	+1 352	+0 49
Glycolamide-lactamide	-0 799	-0 254	+0 54
Glycolamide- <i>a</i> -hydroxycaproamide	-0 799	+1 084	+0 47
Formylglycine-formylaminobutyric acid	-0 330	+0 651	+0 49
Formylglycine-formylleucine	-0 330	+1 556	+0 47
Influence of CH <sub>2</sub> CONH group			
Glycine-diglycine	-3 391	-4 367	-0 98
Glycine-triglycine	-3 391	-4 965	-0 79
Hydantoic acid-diglycine-hydantoic acid	-0 630	-1 533	-0 90
Hydantoic acid-triglycine-hydantoic acid	-0 630	-2 253	-0 81
Glycolamide-glycolylglycine amide	-0 799	-1 517	-0 72
Influence of OH group			
Acetamide-glycolamide	-0 120	-0 799	-0 68
Propionamide-lactamide	+0 016	-0 254	-0 27
Caproamide- <i>a</i> -hydroxycaproamide	+1 726	+1 084	-0 64
Alanine-serine	-2 856	-3 362	-0 51
<i>a</i> -Aminobutyric acid-threonine	-2 375	-3 070	-0 69
Influence of methionyl sulfur			
<i>a</i> -Aminovaleric acid-methionine	1 90*	-2 444	-0 54
Influence of benzene ring			
Alanine-phenylalanine	-2 856	-1 453	+1 40
Influence of dipolar ionization			
Glycine-glycolamide	-3 391	-0 799	-2 59
Alanine-lactamide	-2 856	-0 254	-2 60
Norleucine- <i>a</i> -hydroxycaproamide	-1 414	+1 084	-2 50
Glycine-hydantoic acid	-3 391	-0 630	-2 76
Alanine-alanine hydantoic acid	-2 856	-0 137	-2 72
<i>a</i> -Aminocaproic acid- <i>a</i> -aminocaproic hydantoic acid	-1 414	+1 352	-2 77
Diglycine-glycolylglycine amide	-4 367	-1 517	-2 85
Diglycine-diglycine hydantoic acid	-4 367	-1 533	-2 83
Triglycine-triglycine hydantoic acid	-4 965	-2 253	-2 71

\* Interpolated from *a*-aminobutyric and *a*-aminocaproic acids

the side chains of proteins are polar, the ionic groups and the dipolar ionic structure of proteins must be considered for an adequate understanding of protein behavior

The properties of the proteins must from this point of view be conceived of as depending upon the properties, the number and the distribution of the polar and the non-polar, the ionic and the uncharged groups of which they are composed, of their volumes, their moments, their arrangements in space, and their reactivities with ions and other dipolar ions

#### INFLUENCE OF POLAR AND NON-POLAR GROUPS UPON SOLUBILITY, AND UPON ACTIVITY COEFFICIENTS OF DIPOLAR IONS IN SALT SOLUTIONS

The precipitation of proteins by neutral salts has been employed as a method for "their separation, purification, characterization and occasionally classification"<sup>51</sup> ever since the "procedure was first employed in the middle of the last century by Panum,<sup>52</sup> Virchow<sup>53</sup> and Claude Bernard"<sup>54</sup> Hofmeister demonstrated that "salting-out" depended upon the character of the neutral salt as well as of the protein, and his studies of solubility in concentrated salt solution have since been supplemented by those of Chick and Martin,<sup>55</sup> Sorensen and his coworkers,<sup>56</sup> and by various studies from this laboratory<sup>51 57 58</sup> Certain of the results in concentrated ammonium sulfate solutions are graphically represented in Fig 2 in which the logarithm of the solubility is plotted as ordinate and the ionic strength,  $T/2$ , as abscissa The linear relation that then obtains was demonstrated in 1925<sup>30</sup> and its significance discussed This "salting-out" relation is characteristic not only of proteins but of gases, of uncharged molecules and, in sufficiently concentrated solutions, of electrolytes The problem that remained therefore was to determine which groups, or arrangement of groups, of proteins led to their being readily precipitated, which to their being precipitated only from concentrated solutions of certain neutral salts

On the assumption, implicit throughout this discussion, that amino acids containing the same groups are the prototypes for protein behavior, one may consider the solubility in salt solutions of these smaller molecules of known structure Pfeiffer and his colleagues<sup>59 60</sup> demonstrated that the solubility of leucine was decreased with increase in sodium chloride concentration, but that the solubility of glycine and aspartic

acid was increased. Tryptophane and tyrosine<sup>61</sup> behave much like leucine, but the solvent action of sodium chloride upon asparagine is greater than upon glycine, whereas that of  $\alpha$ -amino-n-butyric acid is but little influenced by low concentrations but precipitated by high concentrations of sodium chloride.

Certain of these results are graphically represented in Fig. 1b. The solubility in water of leucine is so low that solubility ratios may be considered to yield activity coefficients, but that of glycine is so high that a correction must be made for the activity coefficient of glycine in its own saturated solutions (Fig. 1c). The activity coefficient of glycine in sodium chloride, calculated from the freezing point measurements of Scatchard and Prentiss,<sup>62</sup> have therefore been substituted in Fig. 1b for the earlier solubility measurements.

All of the amino acids whose activity coefficients are considered in Fig. 1 are  $\alpha$ -amino acids and therefore have the same moment due to their dipolar ionic structure. They differ from each other only in the length and nature of their side chains. The "salting-out" effect is greatest for leucine which has the largest number of non-polar  $\text{CH}_2$  groups, and begins at low salt concentrations as is the case with such proteins as fibrinogen.<sup>57</sup>

$\alpha$ -Aminobutyric acid with a smaller paraffin side chain is precipitated only from concentrated solutions as is the case with most proteins. That the "salting-out" from aqueous solutions does not depend completely upon the volume of the molecule follows from the comparison of the solubility in salt solution of  $\alpha$ -aminobutyric acid with asparagine and glycine. The two former have almost identical apparent molal volumes,<sup>63</sup> yet the activity coefficient of asparagine is slightly greater than that of glycine, presumably because of the polar nature of its terminal amide group.

Proteins like amino acids may be precipitated from aqueous solution either by organic solvents, such as alcohol and acetone, or by neutral salts, such as phosphates and sulfates. For the amino acids and presumably for the proteins, precisely the opposite groups are responsible for these effects. The order of precipitation is inverted in Figs. 1a and 1b. Molecules with side chains terminating in non-polar groups, though less soluble in the polar solvent, water, are not so readily precipitated by organic solvents as those of the same dipole moment but whose side chains terminate in polar groups. They are however more readily pre-

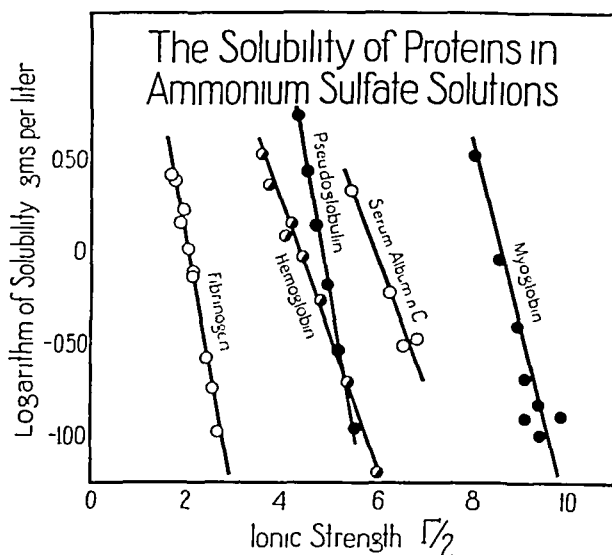


Fig 2

precipitated by neutral salts. Conversely, molecules constituted predominantly of polar groups are more soluble in the polar solvent, water, from which they are precipitated by organic solvents but dissolved by neutral salts, especially by salts of univalent anions and multivalent cations.

#### INFLUENCE OF POLAR AND NON-POLAR GROUPS UPON THE ACTIVITY COEFFICIENTS OF DIPOLAR IONS

The interactions of importance in biological systems are not only those between ions and dipolar ions, but also those between the various ionic and especially dipolar ionic species present as components. The present state of experimental and of theoretical knowledge regarding interactions between dipolar ions in aqueous solution have recently been considered elsewhere.<sup>37</sup> When one of the dipolar ionic species is but slightly soluble, as in the case of asparagine and cystine, solubility methods have been employed in estimating the activity coefficient of one component in the presence of the other. Such knowledge has now been supplemented by freezing point and vapor pressure measurements upon amino acid solutions, and has yielded the activity coefficients of the single solutes as a function of their concentration.

The simplest dipolar ion, glycine, has been investigated both by freezing point<sup>62</sup> and by vapor pressure<sup>64, 65</sup> measurements. The results are in excellent agreement and are graphically represented in Fig 1c.

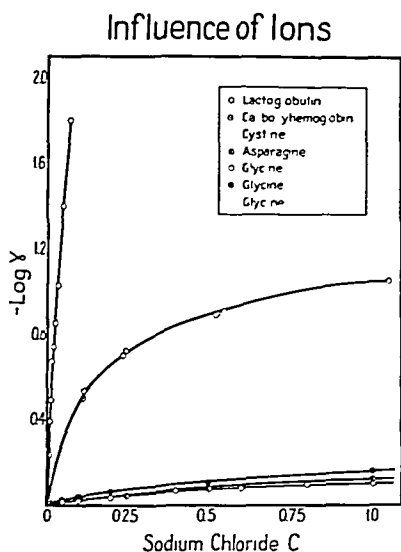


Fig 3a

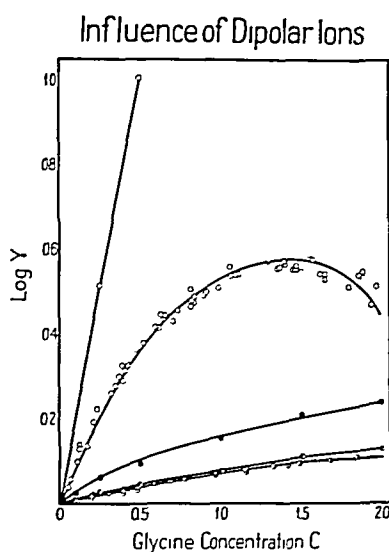


Fig 3b

in which they are contrasted with activity coefficients calculated from vapor pressure measurements for alanine,  $\alpha$ -amino butyric acid and valine. These results may, therefore, be compared with changes in the activity of the same components brought about by neutral salts (Fig 1b). The comparable nature of the forces between dipolar ions and between ions and dipolar ions is evident. The influence of glycine molecules upon each other, or upon other dipolar ions, is superficially not dissimilar to that of sodium chloride (Fig 3). *Dipolar ions with paraffin side chains, however, are "salted-out" by each other much as they are by neutral salts.*

In how far the activity coefficient of a dipolar ion will deviate from unity, in how far its interactions with other dipolar ions or with ions will lead to mutual precipitating action or mutual solvent action, will thus depend upon the balance between its non-polar groups and polar groups, especially its dipolar ionic groups.

#### INFLUENCE OF DIPOLE MOMENT UPON THE ACTIVITY COEFFICIENTS OF DIPOLAR IONS

The polarity of a group is quantitatively measured only in the gaseous state or in non-polar solvents and is generally defined as a displacement of "the center of gravity" of the positive charge from that of the negative charge. The dipole moment is the product of this distance and of



the charge on the electron,  $4.8 \times 10^{-10}$ . The moment of the alcohols due to their hydroxyl group is  $1.7 \times 10^{-18}$  electrostatic units, and that of water is only slightly higher,  $1.87 \times 10^{-18}$ . The esters of the amino acids have been studied in benzene,<sup>66</sup> and the moments and volumes of the groups that we have been considering have been estimated from these and related studies. The moments of urea, amino acids, peptides and proteins are all far higher than these. Urea has a moment of  $5.4 \times 10^{-18}$  electrostatic units, but those of  $\alpha$ -amino acids have been estimated to be approximately 15, of cystine 27, of diglycine 26, triglycine 32, lysyl-glutamic acid 59, of egg albumin 180, of hemoglobin 500, of lactoglobulin 700, and of pseudoglobulin  $1300 \times 10^{-18}$  electrostatic units\* on the basis of dielectric constant measurements.

In the preceding discussion only  $\alpha$ -amino acids or their derivatives have been considered. The distance of separation between the positively charged ammonium and the negatively charged carboxyl group was therefore always closely the same and equal approximately to 3 Å. This distance of separation is, of course, greater in the peptides, and this is reflected by larger dipole moments. In the case of the proteins the magnitude of the dipole moment depends upon the spatial distribution of the ionic groups. Were the cationic groups all at one edge of the molecule and the carboxylic groups at the other, the dipole moments would be many times larger than those observed. On the other hand, were the electrically charged groups arranged with complete electrical symmetry, the molecule would have no dipole moment. All proteins thus far investigated have dipole moments, and if these are small in comparison with what they might be on the basis of the number of ionic groups, and the dimensions of proteins, they are far larger than those of any other known substances.

The interactions of peptides and neutral salts (in regions of low dielectric constant where the "salting-out" effect is small in comparison with Coulomb forces) have previously been reported and demonstrated to increase with increase in dipole moment.<sup>70</sup> Moreover, *the logarithm of the activity coefficient was found to increase by somewhat less than the first power of the dipole moment*.

Neutral salts have a profound solvent action upon the class of proteins termed globulins. This effect, first noted by Denis, was investigated

\* The electric moments of peptides and proteins have recently been considered in detail in the methods of measurement and of calculation are therefore not considered here. The moment of pseudoglobulin is from measurements by J. D. Ferry, Cohn, Oncley and Blanchard.<sup>69</sup>

in 1905 by W B Hardy<sup>71</sup> and by Mellanby<sup>72</sup> for serum globulin, and by Osborne and Harris<sup>73</sup> for edestin. The changes in solubility observed are so large as to form the basis not only for classification but also for methods of purification. Presumably the dipole moments of these molecules are also very large but they have not yet been investigated, nor have preparations of these proteins been available in such a state of purity that their solubility in solution was independent of the amount present in the solid phase.

Hemoglobin and lactoglobulin satisfy this criterion as closely as any proteins thus far investigated. Activity coefficients in aqueous sodium chloride of hemoglobin<sup>51</sup> and lactoglobulin<sup>41</sup> have been calculated from solubility measurements, and are graphically represented in Fig 3 a, where they are compared with those of glycine, asparagine and cystine. As in the case of the peptides, the logarithm of the activity coefficient increases with the dipole moment, and as a first approximation, by slightly less than the first power of the dipole moment.

These results would lead one to conclude that globulins were proteins of high dipole moment. Their low solubility in water presumably inheres, therefore, in very high crystal lattice energies for this class as for the peptides of glycine.\*

The dipole moments of proteins would appear to be one of their most important characteristics, largely defining not only their interactions with neutral salts, but also with other dipolar ions. The solvent action of glycine upon hemoglobin has been investigated by Richards,<sup>64</sup> and upon lactoglobulin by us.<sup>69</sup> Activity coefficients calculated from these results are graphically represented in Fig 3 b in which they are compared with the amino acids, glycine, asparagine and cystine. The similarity in the action of sodium chloride and of glycine is evident, both in the interactions of dipolar ions and of ions and dipolar ions, and  $-\log \gamma$  would appear to increase by something less than the first power of the dipole moment.

The presence of greater numbers of paraffin side chains on the dipolar ions decreases these interactions. The interactions between ions and dipolar ions would also be smaller if, as anions, we considered phosphates, sulfates or acetates, or as cations potassium, rubidium or cesium. On the other hand, they would be greater were the anions bromides or

\* The peptides of glycine are more insoluble the larger the number of glycine residues in the chain. On the other hand, for molecules such as  $\alpha$  and  $\beta$  alanine and  $\alpha$  and  $\epsilon$  aminocaproic acids the isomer of greater dipole moment is the more soluble when there is no difference in density in the solid state.<sup>44</sup>

iodides, or the cations lithium or calcium,\* strontium or lanthanum

### INFLUENCE OF DIELECTRIC CONSTANT UPON THE ACTIVITY COEFFICIENTS OF DIPOLAR IONS

The dielectric constant of a solution may be conceived of as a measure of the dipole moments of the polar groups, and the number of these contained per unit of volume. The dielectric constant of a vacuum is thus unity, and that of the alcohol series is larger the smaller the number of non-polar  $\text{CH}_2$  groups to which the polar hydroxyl group is attached. Indeed it can be shown that the product of the molal volume and the dielectric constant of solutions of the alcohols from heptanol to methanol is essentially constant<sup>38 76</sup> and that this relation extends also to the first member of the series, water, which has a dielectric constant of 78.54 at 25° C as compared with 32.71 for methanol, 24.28 for ethanol and 20.83 for acetone.

But few solvents have higher dielectric constants than water. Among them are hydrocyanic acid and formamide. The latter substance is the first member of the aliphatic amide series, and is in the same relation to acetamide and propionamide as water is to methanol and ethanol. Two of the most polar solvents known, therefore, possess this property by virtue respectively of the hydroxyl and amide groups, both of which, as we have seen, are present in large numbers as constituent parts of protein molecules.

Aqueous solutions of urea have higher dielectric constants than water, and the moment of urea has been estimated, as we have seen, to be  $5.4 \times 10^{-18}$  electrostatic units, or roughly, three times that of the hydroxyl group. The moment of glycine,  $15 \times 10^{-18}$  electrostatic units is, however, three times that of urea, cannot be ascribed to the moments of its polar groups, and is thus evidence of the dipolar ionic structure of the amino acids. The dielectric constant of solutions containing glycine is greater by 23 per mole of glycine per liter of solution. This dielectric constant increment would appear within the limits of measurement to be the same for all  $\alpha$ -amino acids, to be greater by 13.3 for each  $\text{CH}_2$  group separating the positively charged ammonium from the negatively charged carboxyl group, and by 46.0 for each  $\text{CH}_2\text{CONH}$  group separating the dipolar ionic groups in the series of monoamino-monocarboxylic peptides that have thus far been investigated.<sup>38 77</sup>

\* That is assuming that calcium did not lead to a change in the molecular weight of the protein as appears to be the case for casein<sup>74</sup> and certain serum globulin fractions.<sup>75</sup>

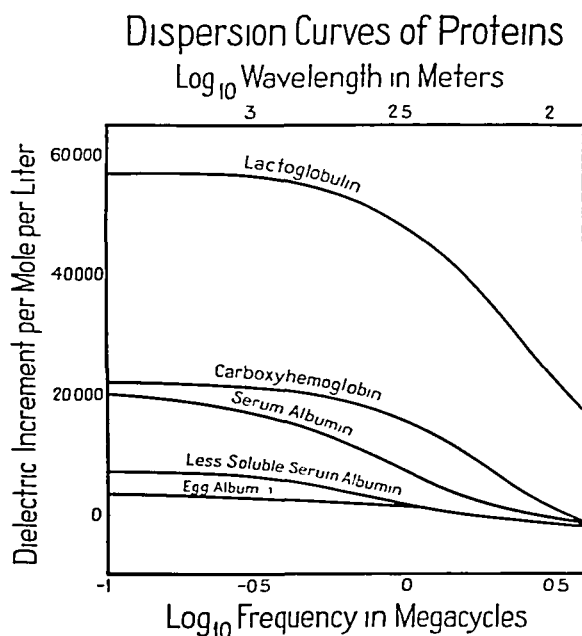


Fig 4

Peptides have been studied which like cystine contain two positively and two negatively charged groups. The dipole moments of such molecules depend upon the spatial arrangement of the charged groups and so do their dielectric constant increments. This is equally true of the multipolar proteins whose moments have been estimated by means of dielectric constant measurements.

Methods of measuring the dielectric constants of protein solutions have elsewhere been discussed,<sup>67 78 79</sup> but the significant results of such measurements may well be considered. Placed in an alternating field the isoelectric protein molecules are oriented by virtue of their dipole moments and the capacity of the system and dielectric constant of the solution is thus increased. The curves in Fig 4 represent this effect, the dielectric constant increments being given by the measurements at low frequency as 3,100 for egg albumin, 22,000 for hemoglobin and 56,000 for lactoglobulin. Of the fractions of crystallized serum albumin that have been investigated<sup>80</sup> the more soluble has a dielectric constant increment of nearly three times the least soluble fraction thus far investigated.

At higher frequencies the large protein molecules can no longer follow the alternating potential and dispersion of the dielectric constant

results. Plotting the measured dielectric constant against the frequency yields dispersion curves of the kind represented in Fig. 4. At sufficiently high frequencies, the dielectric constant measured is actually smaller than that of the pure solvent, and this effect will be greater the larger the volume of the protein which is no longer able to follow the current and the larger, therefore, the number of the smaller solvent molecules which would be able to follow the current at these frequencies, but which are displaced by the protein molecule.

The critical frequencies approximately represented by the midpoints of the dispersion curves are thus characteristic of the size and shape of the protein molecule, and are functionally related to the relaxation times, a quantity which presumably is of significance in electro-physiology. If proteins have different moments but the same size and shape, they will have the same relaxation time, and this would appear to be the case for all the crystalline serum albumin fractions thus far investigated. Molecules of the same size but different shape will, however, have different relaxation times, and this is true among those whose molecular weight lies between 34,000 and 42,000 of egg albumin and lactoglobulin, and among those whose molecular weight lies between 66,000 and 73,000 of hemoglobin and serum albumin. The latter is presumably the more asymmetric and therefore diffuses more slowly, has a higher viscosity and a higher relaxation time.

Measurements of dielectric constant may thus be employed in estimating not only the dipole moments of proteins, but also their relaxation times, sizes and shapes,<sup>26 67 80 81</sup> and may be expected to be of great value in the characterization of proteins. Moreover, the dielectric constant of a solution is one of the most important quantities in determining interactions in which electrostatic forces play a role. The high dielectric constants of protein solutions suggest that many systems of biological importance have high dielectric constants, and that an adequate understanding of interactions in certain cells and tissues demands the development of a chemistry for systems of high dielectric constant.

There is a growing body of knowledge regarding the influence upon ions of substances that increase the dielectric constant of aqueous solutions. The influence of amino acids and proteins upon insoluble salts has been explored by the method of solubility<sup>82 83</sup> and upon soluble salts by the freezing point method,<sup>62 84</sup> or the electromotive force method.<sup>85</sup>

Rates of reaction depend upon the activity coefficients of the reac-

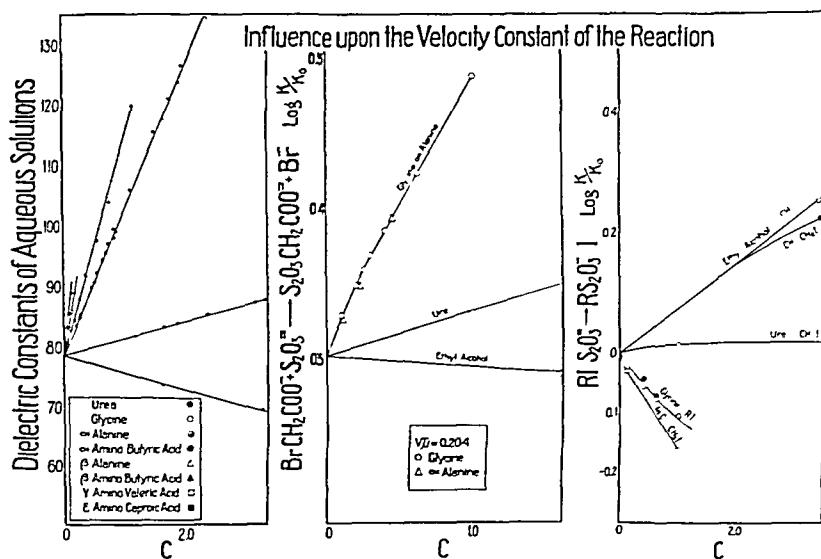


Fig 5a

Fig 5b

Fig 5c

The influence of substances which increase the dielectric constant has been explored upon the reaction of a substance (thiosulfate) on the one hand with uncharged molecules, on the other with ions<sup>86</sup> The rates of reaction with the uncharged molecules, increased by ethanol and to a small extent by urea, were found to be decreased by dipolar ions much as they were by ions (Fig 5c) On the other hand, rates of reaction with ions (Fig 5b) were found to be increased by urea and dipolar ions as well as by ions That the influence upon the rate of reaction was not due merely to change in dielectric constant was demonstrated, however, by the study of solutions iso-dielectric with water The dipolar ions employed were amino acids Those of greater molecular weight and electrical moment, such as are more characteristic of proteins, remain to be investigated, both from the point of view of their influence upon the environment, and of their role as reactants and as enzymes

The lowered activity coefficients of ions in dilute aqueous solution have been demonstrated<sup>87</sup> to depend largely upon electrostatic forces Such forces, according to Coulomb's law, are inversely proportional to the dielectric constant In regions of high dielectric constant, therefore, Coulomb forces are diminished and activity coefficients increased Under these circumstances forces such as those of van der Waals become large in comparison with the greatly diminished Coulomb forces, and differ-

ences in the behavior of ions of the same valence type and of dipolar ions of the same electric moment become apparent \* It is under these circumstances that the so-called Hofmeister series is observed and that great specificity of interaction may be expected

The influence of dipolar ions upon ions and other dipolar ions in systems of many components will thus be to raise the dielectric constant and thereby to diminish electrostatic forces Systems containing ions and two dipolar ionic species are the most complex that have thus far been investigated,<sup>88</sup> but studies upon systems which approach still more closely to those that obtain in nature are in progress, and there would appear to be no differences in principle which should make it impossible to pass from the investigations that have been carried out thus far to the study of interactions between the components of the cells and tissues of the body

### SUMMARY

In order to gain insight into the behavior of even the simplest proteins, we have thus been forced to explore the behavior of molecules of known structure such as the amino acids and peptides Only those proteins have been considered in this discussion which have been isolated in a relatively pure state, and could therefore be investigated as chemical substances The methods would appear to be at hand, however, for the study of all proteins There is no theoretical obstacle to the isolation of all the protein constituents of any given tissue, or to their characterization as chemical substances, and to the study of their interactions as biological components Proceeding thus, often with new techniques, but employing the classical methods of physical chemistry, we may hope in time to achieve an understanding of the morphology and physiology of biological systems in terms of the properties of their components

The description of the proteins of tissues as biological components of known size and shape, the number and distribution of their free groups apprehended and the mechanism of their interactions described remain largely to be accomplished These will depend in many cases upon the spatial configuration of the free groups of the amino acids of

\* Conversely, the lower the dielectric constant the greater the Coulomb forces in comparison with the salting out effect and other non Coulomb forces Under these conditions considered elsewhere<sup>2</sup> the principle of the ionic strength obtains in the interactions between ions and dipolar ions and the valence of the former and the electrical moments of the latter determine behavior

which they are composed, and in others upon the presence of more specialized prosthetic groups

The properties of the proteins as a class permit certain generalizations to be made. By virtue of their large size proteins are retained by cell walls through which oxygen and carbon dioxide, urea and lactic acid, amino acids and many salts freely pass.

By virtue of their ionic nature proteins form salts with each other and with smaller organic and inorganic acids and bases. Certain of these are completely dissociated, others have been judged to be undissociated on the basis of freedom of the non-protein ion to diffuse or to give some chemical test. The precise nature of most of these interactions remains to be investigated.

By virtue of their dipolar ionic structure proteins have high electric moments. These lead, as we have seen, not only to dipole-dipole interactions, but to formation of dipole pairs and to aggregates containing larger numbers of molecules, often arranged with spatial symmetry with respect to each other and dependent upon the shapes of the molecules, the number and distance from the edge of their electrically charged groups and the resulting dipole and multipole moments. As a limiting case the electric moments in the solid state lead to high crystal lattice energies not only in the packing of chemical individuals but of mixed crystals.

By virtue of their high dipole moments proteins contribute high dielectric constants to their solutions. In environments of high dielectric constant Coulomb forces are reduced and conditions obtain that differ widely even from those characteristic of dilute aqueous electrolyte solutions. Although completely dissociated, electrostatic interaction is so reduced that the principle of the ionic strength no longer determines behavior. Under these circumstances, differences in size and shape as well as in valence must be taken into account and non-electrostatic, especially van der Waals forces, acquire primary significance. Under these conditions the behavior of glycine is readily distinguished from that of alanine and of sodium from that of potassium.

By virtue of their high dielectric constants the activity coefficients of both ions and dipolar ions are generally greater than they would be in dilute aqueous solution. As a consequence laws of ideal solution may more often be found to obtain in concentrated biological systems than in dilute aqueous solution. Since rates of reaction are dependent upon



the activity coefficients of the reactants, the high dielectric constant of many biological systems may be expected to play an important role in the kinetics of biological systems

Various laws in terms of which interionic and intermolecular actions may be described are recent contributions of physical chemistry. Many of them are applicable to biological systems in terms of the parameters that have been discussed. It remains to describe in far greater detail the characteristics of the proteins of biological systems as chemical substances and approach ever more closely to the conditions that obtain in biological systems, and which in large part depend upon the highly specialized physical-chemical characteristics of the protein molecule

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fancy than the more recently accumulated physiologic facts would seem to justify I shall, therefore, devote little or no time either to attacking or defending any system of terminology, or in discussing the purely morphologic basis for cell classification. Rather, I shall invite your attention to certain broad, general principles of blood cell growth and blood cell responses, an understanding of which should permit each physician to envisage for himself the underlying hematopoietic and tissue reactions in disease, on the basis of currently obtainable data from the newer types of blood cell *studies* (not "counts")

Five fundamental questions, peculiar to and inherent in hematopoietic tissue, have formed the focus for all of the more recent physiologic studies of the phenomena involving the blood cells (1) the nature and significance of cell origins, (2) the functional specificity and interrelationships of each definitive cell type, (3) the factors essential for differentiation and cell maturation, (4) the forces governing cell delivery and distribution, (5) the conditions influencing cell destruction

#### EMBRYOLOGIC HEMATOPOIESIS

Embryologists are in general agreement that the blood cells derive originally from the mesodermal rather than the ectodermal or entodermal cell layers (Fig. 2). It is also now accepted that the first blood cells to form in the embryo are the red cells, and that they arise intravascularly. Danchakoff<sup>3</sup> and Maximow<sup>4</sup> both affirmed this in 1908 and 1909 using fixed tissues. Sabin<sup>2</sup> in 1920 actually observed in continuous studies of the living chick blastoderm of the second day of incubation, mesoderm differentiating into angioblasts, which in turn gave origin to the first hemoglobin synthesizing cells, the earliest endothelium, and the first blood plasma, megaloblasts, thereafter, arose from and developed within the vascular endothelium of the area vasculosa.

Knoll<sup>5</sup> (1927-29) in a series of thirty-nine human embryos, obtained also in the living state and studied for the development of the hematopoietic tissues, found that the blood contained only red cells through the second month of gestation. Granulocytes appeared about two and one-half months after the red cells, and the lymphocytes still later. Only by the third month were white cells to be seen in appreciable numbers in these human embryos. During the third month the formation of the blood cells is taken over by the liver. By the latter part of the third and during

## ORIGIN OF THE BLOOD CELLS

Presented by thesis

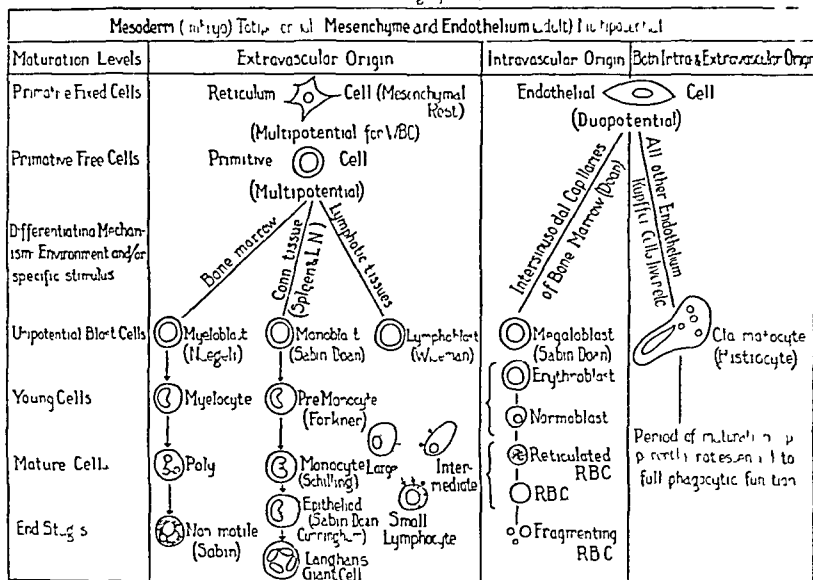


Fig 2

the fourth month changes begin in the cartilage cells in the center of the shaft of the long bones. Vessels from the perichondrium penetrate into the zone of softening cartilage, carrying along connective tissue elements. The primitive mesenchymal cells of the marrow at this stage were accurately described and beautifully illustrated by Maximow<sup>6</sup> in 1910.

## BONE MARROW AS AN ORGAN

In the hypoplastic areas of adult human marrow, this same simple organization of the marrow parenchyma is maintained and when analyzed, the tissue may be seen to be composed only of fat cells, vascular endothelium, and reticulum, i.e. mesenchymal, cells. Such a marrow provides the starting point, as Peabody<sup>7</sup> reemphasized in 1926, for approaching an understanding of cell origins and cell relationships in the more densely hyperplastic areas of active red marrow. According to one school of hematologic thought, as the need for increased red blood cells arises, the fat cells in a quiescent sector are rapidly demobilized, the endothelium lining the intersinusoidal capillaries hypertrophies and divides, with the intravascular appearance of megaloblasts, subsequently these basophilic cells with vesicular nuclei and large single nucleoli, multiply as

they gradually elaborate hemoglobin and eventually form the typical scattered, circumscribed intravascular islands of erythroblasts and normoblasts so characteristic of "red" marrow. Full maturity embodies loss of pyknotic nucleus coincident with development of complete complement of hemoglobin and cell delivery through recanalization of the non-patent erythrocytic capillary. If the need is for granulocytes and thrombocytes, the mesenchymal "rests" (reticulum cells) show increased mitoses with the appearance of myeloblasts and megakaryocytes forming the center of extravascularly located foci of myeloid multiplication and maturation.

### THE LYMPHOCYTE QUESTION

Another interpretation of such hematopoietic activity attributes to one, common, free, stem cell, a so-called lymphocyte, multi- or totipotentialities for all other definitive blood elements. The principal division of opinion at the present time would seem to hinge upon the conception, or the definition, of a "lymphocyte." Probably no amount of discussion, based solely upon morphologic detail, can ever effectively settle the points at issue. There are none of the more distinctive characteristics, such as hemoglobin, specific granules, or patterned vacuoles to differentiate sharply the so-called small circulating lymphocyte of normal blood from other simple, undifferentiated mononuclear elements. Moreover, certain it is that each definitive strain of blood cells originates from a simple, relatively less differentiated, basophilic mononuclear cell, and only gradually evolves or elaborates its distinguishing cytoplasmic and nuclear characteristics. The farther back in the life cycle of any blood or connective tissue cell the hematologic investigator goes, the harder it is to differentiate on morphological grounds alone. Indirect, as well as direct, means must often be utilized in ascertaining essential identifying data. Pappenheim's original concept of a common stem cell, the lymphoidocyte, for all the blood cells, while receiving frequent reaffirmation (Maximow,<sup>4</sup> Danchakoff,<sup>3</sup> Weidenreich, Jordan,<sup>8</sup> Ferrata, Latta and Ehlers, Bloom, Lewis and Lewis) has also been frequently challenged (Ehrlich, Naegeli, Schridde, Schilling, Krumbhaar, Sabin, Cunningham and Doan, Peabody, Clark and Clark, Seeman, Tischtschenko, Hall and Furth). Jordan and his associates in a series of studies (1920-1936) of hematopoiesis in the frog, conclude that the differentiation of lymphocytes originating from reticulum cells gives rise to all of the various types of definitive blood cells. Tischtschenko<sup>9</sup>, on the other hand, working in

His' laboratory in Berlin (1931) concludes that the myeloid and lymphoid elements in frog's blood "must belong unconditionally to two different hemocytogenic systems" Bloom, at the University of Chicago, has cultured the cells from thoracic duct lymph and observed the transformation of large and small lymphocytes into inflammatory polyblasts<sup>10</sup> (1928) and granulocytes<sup>11</sup> (1937) The Clarks<sup>12</sup> (1930) at the University of Pennsylvania, and Seemann<sup>13</sup> (1930) working under Aschoff's direction at the Pathologic Institute of the University of Freiburg, have been unable to interpret in this way their observations, and Seemann, after an extensive cytologic survey in the rat, reports that "the real lymphocyte from lymphatic tissues is not capable of transformation into monocytes and histiocytes," and states, furthermore, that the "extreme monophyletic school of Maximow places under the category of lymphocytes entirely different forms of cells, which are *only separated by supravital staining or biological experiment*" This was the conclusion of Sabin, Cunningham and Doan<sup>14</sup> earlier (1922-1925) working at Johns Hopkins with the supravital technique and *in vivo* animal experimental procedures These investigators defined and differentiated the life cycle of each of the definitive strains of blood cells, ascribing to the specific endothelium lining the intersinusoidal capillaries in marrow the intravascular origin and development of the megaloblast and its progeny, to the extravascular mesenchymal reticulum, the "primitive free cell," lymphocyte-like in size and superficial characteristics, from which the myeloblast, lymphoblast and monoblast derive under appropriate conditions An extended and comprehensive series of experiments followed at Harvard and at the Rockefeller Institute, correlating cell form with cell function under both physiologic and selected pathological conditions, which included the significant studies of Wiseman<sup>15</sup>, all tending to establish the specificity of the life cycle and the functional independence of the so-called small lymphocyte of blood and lymph nodes Hall and Furth<sup>16</sup> (1938) using thoracic duct lymph from normal dogs, and from normal, tuberculous, and B monocyto-genes-infected rabbits, found no evidence in extensive tissue culture studies of any transformation of lymphocytes into monocytes or fibroblasts Occasional monocytes (0.1 to 2.3 per cent) as well as small (85 to 90 per cent), intermediate, and large lymphocytes (5 to 13 per cent) were encountered in the thoracic duct lymph collected for culture In our own laboratory for the past several years, Dr Houghton has been culturing the lymphocytes obtained from pa-



tients with lymphatic leukemia, leuko-lymphosarcoma, and infectious mononucleosis, among materials from other sources, and there has been no evidence adduced in any single instance which could be interpreted as representing a true differentiation of the type of cell recognized morphologically, metabolically and culturally as the "lymphocyte." Rather has the evidence continued to accrue in support of the concept of the functional importance of the lymphocyte *per se* in the body economy as a definitive unit, which frequently serves to antagonize, or reciprocate with, rather than evolve into other cell types.

It would seem, therefore, that the various points of view which have been expressed about the lymphocyte might best be amalgamated and integrated through the acceptance of at least two components as comprising the "lymphocyte" of the monophyletic school: the one, the classical small lymphocyte of blood, lymph nodes and spleen which rarely if ever changes its fundamental form, and the other a comparably small lymphocyte-like, 'blast cell which may always be found associated with active white cell differentiation and maturation anywhere.

Appropriating the universally accepted morphologic criteria of cell maturation common to the better known hemocytogenic cycles, viz., decreasing cytoplasmic basophilia, changes in number, form and distribution of mitochondria, disappearance of nucleoli with progressive elaboration of nuclear chromatin and cell motility, Wiseman<sup>17</sup> divided arbitrarily the circulating blood lymphocytes into three morphologic groups, designated them Young, Mature, and Old, and established their mean frequency and relative proportionate occurrence under conditions of health in animal and human subjects. In normal human adults quantitative values for lymphocytes were observed to range from 750 to 3,000 per c mm., the *qualitative* formula in the average healthy individual being far more constant: Y M O 4 48 48. Thus, although the number of circulating lymphocytes fluctuates widely in health from person to person and in the same individual from time to time, the proportionate age relationships, based upon the morphologic characteristics cited, remain much more constant and have seemed to change significantly only when disease intervenes. From the evidence available, Wiseman has assumed that the absolute number of lymphocytes present in the peripheral blood at any one moment is the resultant of the balance between four major forces: (1) the speed and efficiency of differentiation and maturation of lymphocytes within the follicles of the lymph

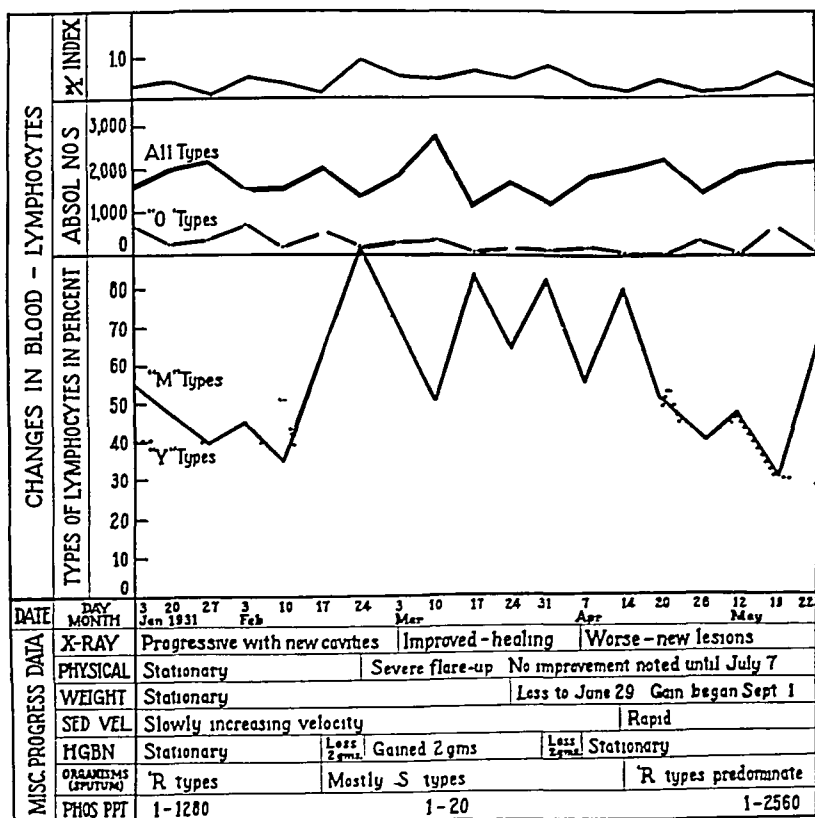


Fig 3

W I white male aged 22 years with known clinical tuberculosis of 3 years duration and a sanatorium history of 11 months X ray diagnosis far advanced active tuberculosis with multiple cavitation The clinical and laboratory findings are recorded The Y M O qualitative relationships within the lymphocyte strain of cells changed markedly during the 5 months of observation reflecting more sensitively than any other single criterion the patient's reaction to his disease

nodes, (2) the rate of delivery of these cells to the circulation, (3) the rapidity of their withdrawal or destruction, reflecting changing functional demands or toxic influence, (4) the capacity for reservoir storage of lymphocytes in the tissues It is entirely conceivable, and in practice it has been found to occur, that a profound imbalance in the lymphopoietic equilibrium may occur without alterations in the total circulating lymphocytes, beyond the rather wide limits established for normal individuals, quite as has been recognized for the neutrophilic granulocytes since the analyses of Arneth, Schilling, and a host of subsequent observers This relative age-maturity interpretation of the finer differentiating qualitative criteria observed in fixed and supravital stained films of

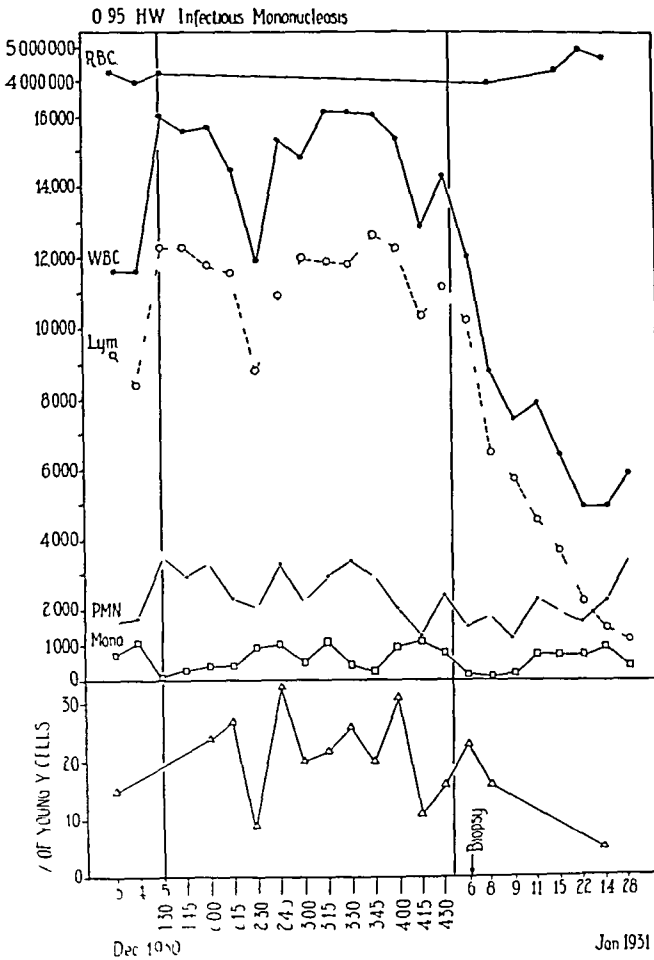
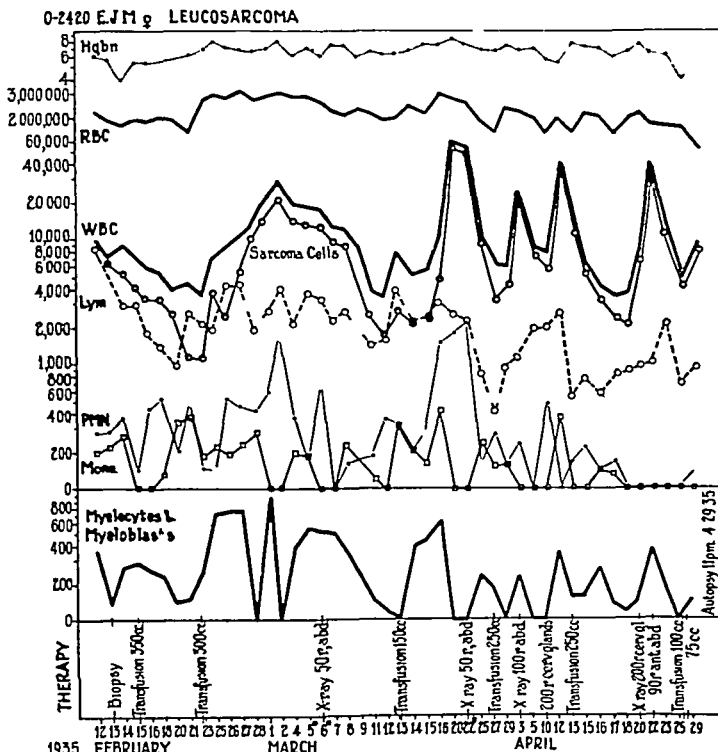


Fig 4

The young relatively large, lymphocyte with Reider nucleus, which usually dominates the blood picture in infectious mononucleosis is pathognomonic of this benign dyscrasia. Serial, 15 minute interval counts were made during the period indicated on Dec 5 to demonstrate the physiologic correlation (non-leukemic) between the fluctuations in the total lymphocyte count and the corresponding proportion of "young" lymphocytes. As the disease subsided and the lymphocytes returned to normal in number and quality the neutrophils, which had been moderately depressed returned to their normal number and relationship in the differential count.

normal blood could, of course, only be established and then applied clinically by submitting the hypothesis to experimental and practical tests under known conditions. This Wiseman has proceeded to do. In rabbits injected with foreign proteins or inoculated with bovine tubercle bacilli the profound disturbances in lymphocytes—reciprocal to granulocytes in the former instance and to monocytes in the latter—were only fully understood and could only be adequately correlated with the final tissue studies by recognizing and interpreting the qualita-



\*Micrometabolism of blood cells performed on these dates

Fig 5

In leucosarcoma two distinct types of lymphocytes may be seen side by side in the same microscopic field the one normal mature according to every criterion the other obviously a much younger form with large single nucleolus and characteristic cytoplasmic changes when observed with supra vital stains Deep x ray therapy in very small dosage destroys promptly the sarcoma lymphocytes while depressing little if any the normal lymphocytes A myelophthisic blood picture with anemia nucleated red cells myeloblasts and myelocytes reflects the hyperplasia of leucosarcoma cells in the bone marrow Micrometabolic studies have shown a malignant type of respiration for the sarcoma cells in sharp contrast to the data obtained from normal and leukemic lymphocytes

tive, in addition to any quantitative changes in the lymphocytes In human tuberculous patients (Fig 3),<sup>18</sup> in infectious mononucleosis, (Fig 4), in leuko-lymphosarcoma (Fig 5), in chronic lymphatic leukemia (Fig 9),<sup>19</sup> the importance, significance and validity of the qualitative differentiation of the lymphocytes has been clearly established The interpretations based upon these morphologic criteria in the circulating lymphocytes have been validated by and correlated with basal and cell metabolic studies, specific cell motility characteristics, by observed variations in cell behavior in tissue culture, and by contrasting biopsy and postmortem tissue That is to say, the human blood lymphocyte shows a

variety of characteristic cellular alterations more or less pathognomonic of various disease mechanisms, but always it retains sufficient criteria to identify it with its own definitive maturation cycle

### THE GRANULOCYTES

Turning now to the granulocyte, a much more readily recognized maturation cycle may be seen in normal bone marrow. The agranular myeloblast has a less deeply basophilic cytoplasm than the germinal center lymphoblast, fewer and finer mitochondria, and a nucleus usually with more nucleoli. Seldom need the trained cytologist hesitate in differentiating lymphoblast and myeloblast. The more primitive free cell common to lymph node, bone marrow, and connective tissues<sup>14</sup> and only observed under conditions of excessive stimulation in one or other of these areas, is the cell, if any, which will be confused with the small lymphocyte of suspected multipotential capacities of differentiation. As soon as the first specific granules appear in the myeloblast—neutrophilic, eosinophilic or basophilic—the respective definitive cell type may be predicted. Coincident with granule appearance, but not before, neutrophilic and eosinophilic myelocytes become oxidase reactive, the amount of the peroxidase precipitate being directly proportional quantitatively to the number and size of the granules present in any given cell<sup>20</sup>, basophil granules remain oxidase negative throughout the basophil granulocyte life cycle. Lymphocytes throughout their life cycle and in their various pathologic responses, and all “primitive” and ‘blast blood cells remain oxidase negative. All myelocytes lack intrinsic motility until maturity under normal circumstances, which is to say, from the morphological standpoint, until a full complement of specific granules has been developed, the basophilia and mitochondria of the cytoplasm have gradually diminished to the vanishing point and the nucleoli have disappeared and the chromatin greatly condensed in a nucleus which is beginning to constrict preparatory to lobulation. In acute infections and under certain other pathologic conditions, motile, granule-deficient neutrophilic leukocytes with mitochondria and basophilic cytoplasm, may be encountered. Throughout the myelocytic phase of maturation, the cytoplasmic criteria are the more dependable, especially granule development, less than ten specific granules per cell being designated myelocyte A, approximately 50 per cent granules, myelocyte B, and a full complement of granules, myelocyte C<sup>21</sup>. During this inverse reciprocal evolution in

mitochondria, cytoplasmic basophilia and specific granule formation, the nucleus becomes smaller, more pyknotic and finally segments. Ameba-like motility ensues with a liquefaction of the hitherto gel-like cytoplasm, and the relative age of the motile mature granulocyte is thereafter gauged by the number of lobes to the nucleus (Arneth<sup>22</sup>). The origin of the myelocytes being extravascular in the parenchyma of the bone marrow in the normal human adult, and the function of the mature granulocytes being accomplished in remote tissues or along the mucous surfaces of the body, intrinsic cellular motility is a prerequisite to the entrance of the leukocytes into, and their egress from the blood stream, except on occasions secondary to pathologic marrow hyperplasia.

#### THE MONOCYTE-CLASMATOCYTE RELATIONSHIP

The monocyte or "transitional" of Ehrlich has been almost as difficult a cell to accept and to assign specificity and independence as the lymphocyte. First, its azurophilic granules in a mottled basophilic cytoplasm with oval or slightly indented vesicular nucleus were thought to represent an earlier stage in the maturation of the myelocyte, later the azur granules of the lymphocytes were thought to be identical with them.<sup>23</sup> In 1913 Schilling<sup>24</sup> first declared that the criteria were sufficient to establish the monocyte as an independent and distinct cell entity, and the development and application of the supravital staining technique to this problem of cytologic specificity subsequently has fully supported the rightness of Schilling's conclusions. A cytoplasmic system of vacuoles was revealed in the living cell, which stains characteristically with neutral red, is arranged as a rosette opposite the *hof* of the nucleus, and is surrounded by mitochondria, all of which methyl alcohol obliterates from the ordinary fixed stained blood films. Furthermore, a characteristic surface film type of motility differentiates the monocyte in fresh preparations from both granulocyte (ameboid) and lymphocyte (peristaltic). Here again, a careful study of the peripheral nodes<sup>25</sup> and spleen,<sup>26</sup> where monocytes arise normally, and more especially the analysis of experimental monocytoses<sup>27</sup> establishes a maturation sequence from primitive, basophilic, non-vacuolar, non-motile, monoblast through succeeding stages of nuclear and cytoplasmic development to characteristic mature, motile monocytes. Under pathological conditions, such as tuberculosis, the monocyte may be altered by the bacterial lipids<sup>28</sup> to become the typical epithelioid cell and Langhan's giant cell of the tissue tubercle.

Now, morphologically and functionally distinct from the other circulating leukocytes by common consent, the monocyte still must share the connective tissue role of phagocytosis and thereby merge its identity, in the opinion of some, with the tissue macrophage or clasmatocyte. Whether these functionally and histologically similar, but not morphologically identical, cells represent different phases in the life cycle of the same cell, or whether there are two tissue phagocytes of different origin remains today a matter of debate and further experimentation. The evidence from supravital studies of experimental and pathological tissues favors the independent origin and separate identity of monocyte and clasmatocyte (Fig 2), though recognizing at times their common response and similar behavior in non-specific tissue reactions. The clasmatocyte is the one cell of the tissues, and/or rarely of the blood, which does not seem to require a period of maturation for full functional activity.

So long as abstract static morphologic studies alone were made of the complex medley of multiple cell types, each with its own complicated life cycle, little progress of functional or clinical significance was possible, only unverifiable speculation existed. However, with the acquisition of increasingly distinctive criteria of type and age specificity, and with the means and the interest to analyze and interpret a variety of induced and spontaneously occurring cellular *disequilibria* in terms of functional responsiveness and relative tissue adequacy, substantial physiologic information of great significance has become available, and facts are slowly beginning to fortify or undermine fancies, as the case may be. With the newer knowledge, of fundamental mechanisms and inhibiting and stimulating influences upon blood cell multiplication and maturation, the formulation and application of rational prophylactic, as well as therapeutic regimes, has become possible.

### ERYTHROPOIESIS

In no area of specific or general health is this more true than that of the oxygen-carrying mammalian red blood cell. Other than a relative degree of regional anoxemia, we do not yet know the additional fundamental requisites for the primary initiation of erythrogenic differentiation. When we do, the answer to some of the "primary" aplasias will probably be known. Many toxic substances will inhibit or destroy normal erythropoiesis, such as benzol, arsphenamin, x-ray, and radium,

and when promptly recognized and eliminated, recovery ensues. A congenital accentuation of physiologic splenic hemolysis may disturb the hemolytopoietic equilibrium to the point of acute hemoclastic crisis, the bone marrow is hyperplastic, usually at the late erythroblast and normoblast level of maturation, and successful splenectomy initiates a prompt erythrocyte reequilibration, with complete clinical recovery.<sup>29</sup> In iron deficiency states, a hypochromic, microcytic anemia, with low plasma iron,<sup>30</sup> without intrinsic marrow defect may be remedied specifically through adequate replenishment of the body's depleted iron reserves. In such an instance no diminution in number of circulating or marrow red cells need exist, but iron must be available for the synthesis of hemoglobin. Vitamin C and thyroxin are also essential to the maintenance of normal erythropoietic equilibrium. When maturation arrest occurs at the megaloblastic level of red cell differentiation, an hyperplasia develops in the marrow with progressive peripheral anemia, hyperchromic and macrocytic in type. The life cycle of the erythrocyte is best observed while following the recovery from such a state (Fig. 6). Because of inability to utilize iron without the erythrocyte maturation factor, plasma or transport iron values are higher than normal.<sup>30</sup> Coincident with the supplying of this deficit by any one of a number of oral or parenteral sources of the active principle, iron once more is utilized in considerable quantities, reflected by a precipitous fall in the plasma iron level in direct relationship to the maturation, and, therefore, prompt disappearance of the megaloblasts as such from the marrow, in their place appears a transitory increase in early erythroblasts to be followed promptly by late erythroblasts with still more iron containing hemoglobin until, finally, by the fifth or sixth day, normoblasts dominate numerically the age-range of the nucleated red cells in the marrow with only a minimal number of the less mature erythroid elements still present. In the peripheral blood the reticulocytes usually reach their peak some 24 to 48 hours after the normoblasts have become the predominating red cell in the marrow, representing the youngest of the enucleated red cells in the circulation, and marking the culmination of the suddenly reestablished maturation cycle. As erythrocytic equilibrium is again approached, the reticulocytes fall to their physiologic level of less than 1 per cent, and the marrow gradually resumes its normal cellular relationships, permitting the myelophthisically depressed platelets and granulocytes to regain their accustomed levels. In the patient



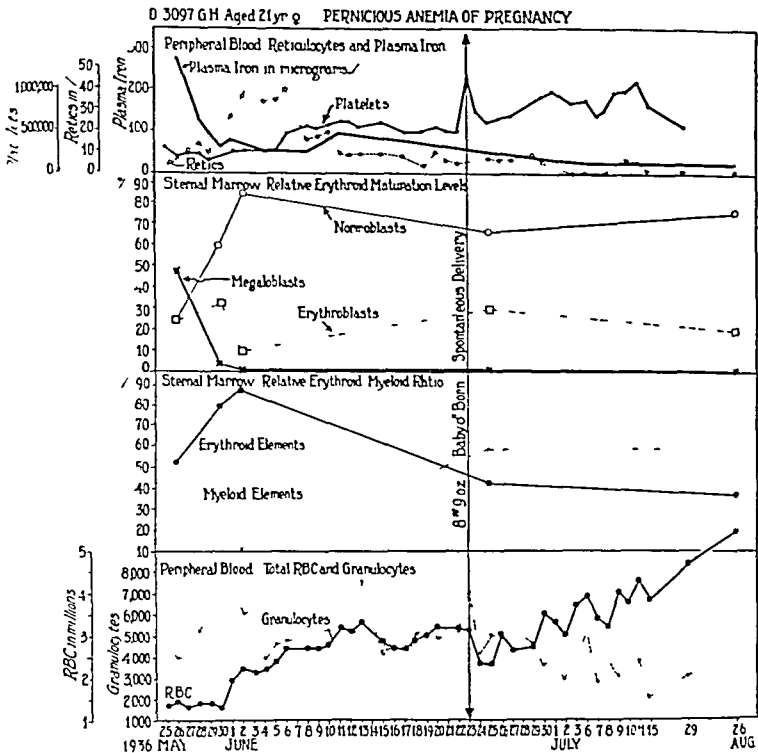


Fig 6

Extrinsic factor dietary deficiency during the fifth successive pregnancy in as many years resulted in a macrocytic anemia in this patient indistinguishable as to peripheral blood picture hyperplastic megaloblastic marrow and high plasma iron from Addisonian pernicious anemia. Gastric analysis revealed 68° free HCL. The institution of a high caloric protein diet plus 50 gms autolyzed yeast daily brought about a prompt utilization of the excessive circulating plasma iron this was reflected immediately in the bone marrow by increased hemoglobin synthesis which reduced the proportion of megaloblasts the resulting erythroblasts in turn gave way to normoblasts to be followed by the usual reticulocyte peak in the peripheral blood. With the reduction in marrow erythroid hyperplasia platelets and granulocytes returned to their normal levels and with the reestablishment of a normal red cell and hemoglobin equilibrium plasma iron and reticulocytes became normal and the erythroid myeloid ratio in the marrow became physiological. An identical maturation sequence has been observed in repeated instances of adequately treated primary pernicious anemia with intrinsic factor deficit.

illustrated in Fig 6, the approximate length of time for maturation from megaloblast to non-reticulated mature red blood cell might be estimated at 15 days, on the basis of the available data. Jones<sup>31</sup> has described the megaloblast and its interrupted maturation in Addisonian pernicious anemia as a distinctly abnormal pathologic phenomenon, bearing no relationship to, and having no counterpart in, embryologic or normal adult erythropoiesis. This has not been the interpretation of Dr Sabin and her associates, who rather consider the macrocytic deficiency anemias to represent the result of a metabolic deficit compar-

able to the simple iron deficiency states, in which no inherent bone marrow pathology as such exists. The functional inadequacy of marrow is secondary to gastrointestinal or liver pathology, the last-named assumes primary etiologic significance in the light of Castle's, Whipple's and Minot's classical observations. Given suitable erythrocyte maturation factor, an entirely normal bone marrow, histologically and functionally, results promptly.<sup>32</sup>

### HEMOCYTOLOGIC RECIPROCITIES

Although many of the same noxious agents which depress erythropoiesis may inhibit or destroy granulocytes and lymphocytes and interfere with thrombocytopoiesis, it has become increasingly apparent that highly specific effects, either stimulatory or inhibitory, may be limited solely or largely to one cell strain. There is also evidence that significant reciprocal cell-strain relationships frequently result as a part of pathologic reactions.<sup>33</sup> The simplest and most readily understood example of marrow cell reciprocity is that just cited of the mechanical limitation of myelopoiesis and thrombocytopoiesis in pernicious anemia in relapse secondary to megaloblastic hyperplasia. The same diminution in normal number of circulating blood elements, with characteristic "left shift" qualitative alterations in the cells, is seen in multiple myeloma, metastatic carcinoma, osteosclerosis, leukosarcoma, the leukemias, or in any condition where such an abnormal appropriation of marrow parenchyma restricts the origin and development of normal hemopoietic foci. The remedy for specific blood cell insufficiencies resulting from these causes, lies obviously in restricting the abnormal cell growth and not in the institution of hemopoietic therapeusis *per se*.

However, more subtle reciprocal relationships among the blood cells have been observed which have a direct bearing upon the question of cell origins and their developmental potentialities and specificities. From the experimental angle it has been found that the amphophilic (neutrophilic) granulocytes in rabbits may be strongly stimulated by the nucleic acid derivatives and their components, the nucleotides, specifically, adenine and guanine.<sup>34</sup> A general myelocytic marrow hyperplasia resulted, and under prolonged stimulation ectopic foci of myelocytes were found in spleen and kidneys.<sup>35</sup> It was noted during these studies that the total number of circulating lymphocytes decreased as the granulocytes rose, and at postmortem the lymph nodes, spleen and

other sites of lymphoid development were found to be practically devoid of all follicles and all germinal center activity<sup>33</sup> No myelopoietic activity and no myelocytic infiltration had occurred in these areas, so that the atrophy appeared to be the result solely of spontaneous, reciprocal lymphocytic hypoplasia. Conversely, the administration of foreign protein to rabbits<sup>17</sup> resulted in a marked increase in circulating lymphocytes at the expense of granulocytes, the latter falling as low as 400 per c mm during the peak of lymphocytosis. Autopsy surveys showed an extensive, marked, generalized hyperplasia of all lymphoid tissues including a greatly enlarged spleen, while the bone marrow everywhere showed a marked myelocytic hypoplasia extending to complete aplasia in some normally active areas.

Simple, uncomplicated, hypertherm- or radiotherm-induced fever in rabbits has been found to influence myelopoiesis favorably while at the same time destroying lymphocytes and inhibiting their regeneration temporarily.<sup>36</sup> A progressive "left shift" in the nuclear index of the circulating granulocytes was correlated with prompt progressive, myeloid hyperplasia and increased mitotic activity in marrow, and a marked immediate postfebrile leukocytosis, conversely the peripheral lymphopenia reflected a progressive cellular destruction necessitating increased clasmatocytic phagocytosis without regenerative replacement wherever lymphocytes were located in the tissues, with a prolonged latent postfebrile period before lymphopoiesis could again become effectively re-established.

In each of the instances cited, one particular cell strain was markedly responsive to a stimulus, which at the same time, either directly or indirectly, influenced adversely another supposedly closely related cell type. It might seem that were the granulocytic cells directly dependent upon the lymphocyte of blood and lymph nodes for their origin and differentiation, any influence subversive to lymphocytic integrity would likewise be reflected in a diminished production and supply of granulocytes to the organism. Or, if an unusually prolific supply of multipotential lymphocytes became available, there would presumably be no obvious reason for a reciprocal decrease in the direct progeny of such a stem cell, rather some corresponding increase in granulocytes might be anticipated. Quite the opposite has been observed in the experimental field.

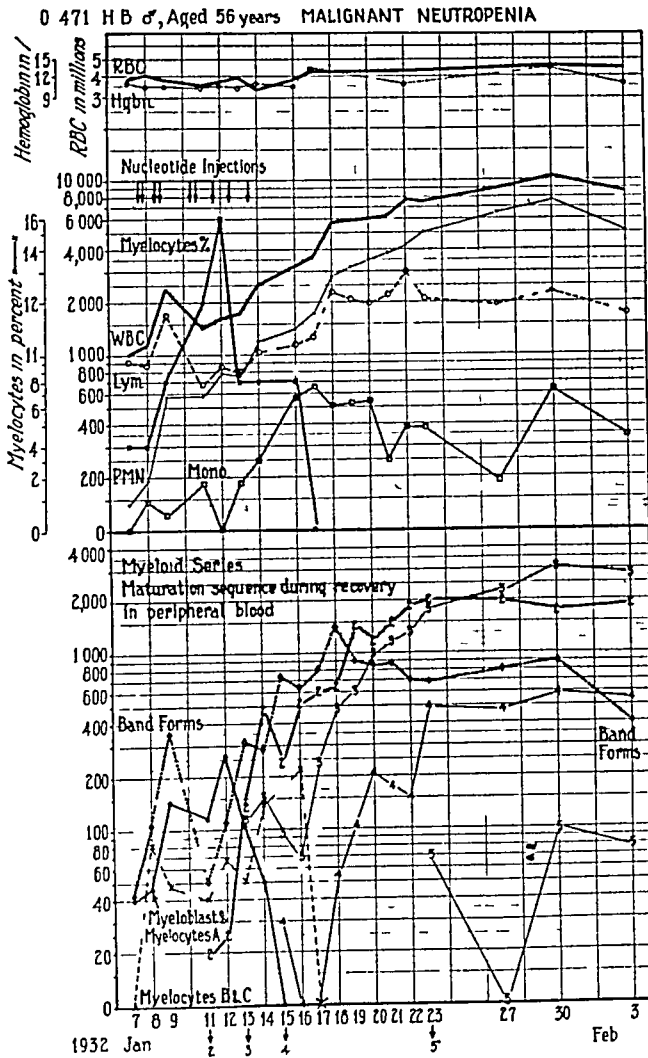
Is there, then, any counterpart in the cellular disequilibria occur-

ring during the clinical course of human disease, which might permit of interpretations in one direction or the other concerning fundamental cell origins and cell relationships? In infectious mononucleosis a marked lymphocytosis (Fig 4), both relative and absolute, usually occurs with characteristic qualitative changes in this cell strain, associated with a more or less generalized lymphadenopathy. A reciprocal granulopenia has been observed, resulting not infrequently in a profound decrease to 500 or less granulocytes per c mm, the sternal bone marrow showing at such times an absolute decrease in myelocytes.<sup>33</sup> Clinical recovery is not complete until the disturbed cell relationships in the blood and tissues have been corrected.

#### THE MECHANISM AND SPECIFICITY OF CELL STIMULATION AND CELL INHIBITION

Turning to the problem of acute granulopenia in human disease, the nucleotides may be said to have the strongest and most powerful chemotactic and maturative stimulus for neutrophilic granulocytes of any agent thus far studied. In patients with the Schultz syndrome,<sup>37</sup> if monocytes remain present in the peripheral blood and the sternal bone marrow is not entirely aplastic for myeloid elements, recovery more often than not parallels the administration of pentnucleotides. This statement is made with full realization of the establishment of a specific hypersensitive destructive and inhibitory etiology for amidopyrine and certain other drugs in certain specific myelopenic states, with the desirability and necessity of prevention in these cases. In all leukopenic patients, in which the etiology is not immediately obvious, however, a knowledge of the state of the bone marrow is essential to intelligent therapy today. Usually this information may be obtained quite as satisfactorily by sternal puncture as by surgical trephine. The principal requirement is a familiarity with the morphologic characteristics of the maturation cycle of each strain of cells found normally in bone marrow and with the relative proportions of each as revealed by actual differential cell counts of representative marrow samples.

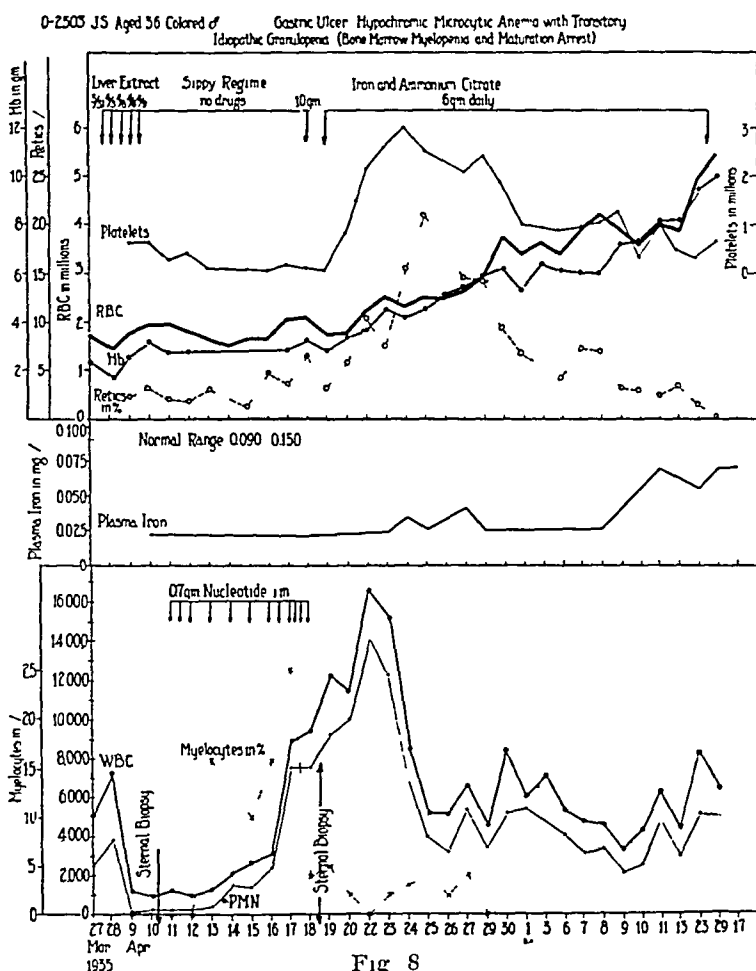
When the peripheral leukopenia is found to be secondary to both a maturation arrest and an inhibition of marrow myelopoiesis, the recovery, if it occurs, is reflected by changes in the granulocytes, which are entirely comparable to those observed in the red cells during the recovery from relapse in pernicious anemia. Depending upon the degree



This, in detail is the peripheral blood reflection of bone marrow recovery in a classical acute neutropenic episode of undetermined etiology. There appeared sequentially in the blood every stage in the entire life cycle of the neutrophilic granulocyte from myeloblast to mature five-lobed polymorphonuclear, the myelocyte percentage rising to a peak and then dropping sharply in duplication of the reticulocyte phenomenon illustrated in Fig 6. From such observations it is estimated that it may take as long as 16 days for maturation from myeloblast to five-lobed neutrophil and that regeneration must take place in some instances at least from the myeloblast level.

of myelocytic immaturity which prevails at the time of the reactivation of the marrow, there will appear transiently in the peripheral blood, myelocytes in increasing percentage, comparable to a reticulocyte peak.<sup>38</sup> Moreover, the maturation sequence from myeloblast through myelocytes A, B, and C may be followed both in serial marrow punctures and in the daily white cell differential counts. In one such patient

(Fig 7), when first seen in an acute granulopenic episode with less than 1000 leukocytes per c mm (erythrocytes and thrombocytes normal), myeloblasts and myelocytes A were present in the peripheral blood. During the days following the institution of nucleotide therapy, there appeared a maturation sequence in the circulating myeloid elements, which reflected accurately the steps of recovery in the marrow. The myeloblasts and the earliest myelocytes with the first few specific granules increased to their highest point of 280 per c mm on the fifth day of treatment, disappearing on the eighth. Myelocytes B and C, containing a more complete complement of specific granules, were present at the end of the first 24 hours, reached their maximum of 250 on the ninth day, and had disappeared by the following day. The "band forms" of Schilling, the youngest of the motile mature granulocytes, were present to the number of 40 per c mm on the first examination and were found in all preparations at all times, but did not show any sustained absolute increase until the eighth day, reached their peak of 1400 on the eleventh day, and thereafter gradually decreased to resume their proportionate representation as equilibrium was again established. The first granulocyte with a segmented nucleus, two lobes, was observed on the fourth day, and thereafter these two-lobed neutrophils increased steadily until the twentieth day, when the three-lobed granulocytes, which had been present since the sixth day, finally surpassed them in total number. One cell with four lobes to the nucleus was seen in one preparation on the eighth day, but not until the eleventh day were they permanently present. Five days later, on the sixteenth day following the beginning of recovery, granulocytes showing five nuclear segments appeared, at which time the total granulocytes had increased from their original low of less than 100 to something over 5000 per c mm. Thus, from myeloblast to five-lobed polymorphonuclear neutrophilic leukocyte required approximately 2 weeks' time in this individual. With increasing maturity of the circulating myeloid cells came increased absolute numbers, reflecting both a specific myelopoietic inhibition and maturation arrest in the marrow during the fastigium of clinical symptoms. The episode described, occurred in January, 1932 unrelated to any determinable drug etiology, and though two less severe leukopenic relapses occurred during the following two years, associated with severe emotional environmental stresses and strains this physician-patient is still living and well at the time of this writing, with no evidence of hemo-



Demonstration of the complete independence of myelopoietic and erythropoietic responses to specific therapy in an individual developing an acute idiopathic granulopenia while in the hospital under observation for a severe anemia secondary to bleeding peptic ulcer. Liver extract neither helped the anemia nor prevented nor "cured" the neutropenia. The extremely low plasma iron reflects the exhaustion of the body's iron reserves from chronic hemorrhage resulting in a typical, microcytic, hypochromic anemia. Note different time relationships in the administration of the various therapeutic agents and the corresponding cellular responses including the platelet increase which accompanied the erythroid recovery. See Table I for the actual differential counts of blood and sternal marrow cells April 10 and 18.

poietic marrow inadequacy

The specificity of the inhibition of marrow myelopoiesis in these clinical instances of granulopenia has been stressed, thus emphasizing two significant points with reference to the physiology of bone marrow as an organ, namely, the probable independence of the respective stem cells from which erythrocytes and granulocytes normally arise throughout postembryonic life, and, an obvious corollary, the specificity of the responses to both depressants and stimuli of these respective cell strains. Fig 8 and Table I further support these conclusions. During

TABLE I

(To be studied in conjunction with Fig 8 and the text)

# NUCLEOTIDE-TREATED IDIOPATHIC NEUTROPENIA (maturation arrest)

## Serial Sternal Bone Marrow Biopsies

Patient J S Aged 36 years, colored, ♂  
 Diagnosis 1—Gastric ulcer—hypochromic microcytic anemia  
 2—Idiopathic granulopenia, acute, transitory (no drugs)

April 10

1935

April 18

## BLOOD

Total WBC	925		9400
Total RBC	1,700,000		2,090,000
Hemoglobin			2.8 gm /100 cc
(Newcomer)	2.5 gm /100 cc	PMN	81% Lym small 8%
Supravital Diff	Only 1 2-lobed PMN found	PMB	1 int 1
		Myelocytes	3 Monocytes 6

## BONE MARROW

Supravital Diff	First Biopsy		Second Biopsy	
PMN	13	4%	76	14%
Metamyelocyte	6	1%	68	12%
Neutrophilic "C"	30	9%	360	67%
	15%		94%	
"B"	246	71%	32	6%
"A"	51	14%	0	0%
	85%		6%	
Basophilic "C"	1		12	
"B"	13		4	
"A"	10		2	
Eosinophilic "C"	1		8	
"B"	1		2	
"A"	0		0	
Myeloblast	1		0	
Lymphocyte	2		0	
Monocyte	1		2	
Chromatocyte	16		4	
Primitive Cell	0		0	
Total WBC	392	36%	572	54%
Normoblast	595	87%	334	75%
Erythroblast	62	9%	116	24%
Megakaryoblast	23	3%	4	0.8%
Total RBC	680	64%	474	46%
Cells counted	1072		1046	

84 gm nucleotide given in 8 day period



hospitalization, incident to a severe hypochromic, microcytic anemia secondary to bleeding peptic ulcer, there developed in this patient an acute granulopenic episode. Sternal biopsy proved the accuracy with which the peripheral blood was reflecting the underlying marrow pathology. Only 36 per cent of all nucleated marrow elements were of the myeloid series and 85 per cent of these were the very young myelocytes A and B, a distinct "left shift" from the normal maturative relationships. The nucleated red cells (64 per cent of all marrow elements) were predominantly (87 per cent) at the normoblastic level, which is representative of the maturation level when no inadequacy in the erythrocyte maturation factor prevails, and explains the lack of response to liver extract, given as a control. Eight days later, when the granulocytes had increased in the peripheral blood from practically zero to 8000 per c mm, a second sternal biopsy from another interspace revealed a corresponding change in the age and proportionate representation of the myeloid elements without significant qualitative alteration in erythropoiesis or circulating erythrocyte level. The myelocytes represented 54 per cent of all nucleated cells at this time, and of equal or even greater significance was the increase in the relative proportion of the more mature myelocytes C and metamyelocytes from 15 per cent to 94 per cent. During this change in the number and maturity of myelocytes in the marrow, the peripheral blood was showing a myelocyte peak with a high of 25 per cent reached on the seventh day following institution of nucleotide therapy, preceding the absolute increase in total circulating granulocytes, much as does the reticulocyte rise following specific therapy in the anemias. During this episode, erythrocytes and hemoglobin remained stationary. However, with the institution of adequate iron therapy in this patient, a typical reticulocyte response was elicited, reaching a high of 21 per cent on the seventh day followed by a rapid return to normal in plasma iron, total red cells and hemoglobin. No further hematologic disturbances have been observed in this patient.

The occasional chronic lymphatic leukemia patient will have a bone marrow hypoplastic for myelocytes unassociated with lymphocytic hyperplasia or infiltration. In such a case<sup>30</sup> it was possible to stimulate a rise in neutrophilic granulocytes from a few hundred to 10,000 per c mm, with daily injections of the nucleotides (Fig 9). No demonstrable effect on the lymphocytes was observed, suggesting the essen-

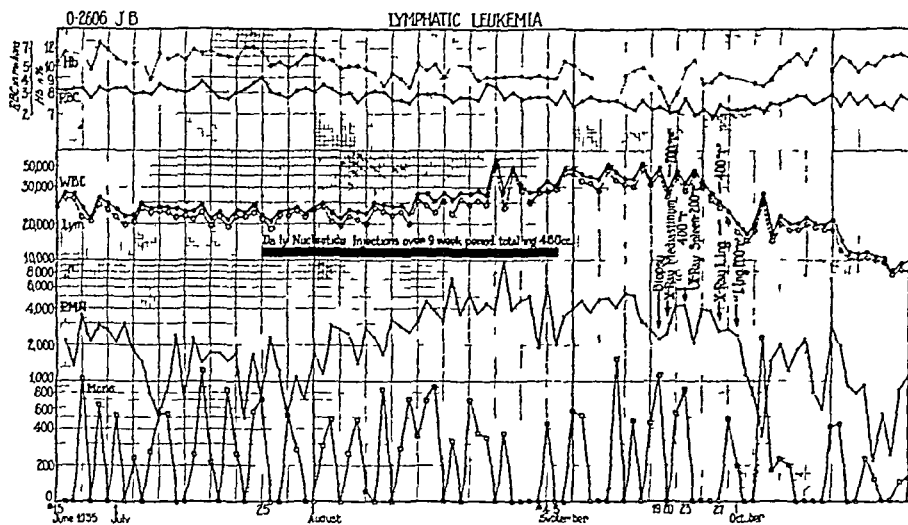


Fig 9

A patient with chronic lymphatic leukemia with reciprocal granulopenia as low as 500 neutrophils per cmm during 9 weeks of daily nucleotide injections showed a gradual but steady increase in these elements to 10 000 per cmm. During this period there was no reciprocal fall in the leukemic lymphocytes but rather a slow uninterrupted increase which continued until deep x-ray therapy was administered. The polymorphonuclear neutrophils failed to continue their upward trend as soon as nucleotide therapy was discontinued and subsequently fell to their previous low level indicating the specific character of the stimuli and independent capacity to respond of these two cell strains.

tial independence of lymphocytic and myelocytic responses, at least under certain circumstances. The same fundamental observation has been made relative to lymph node atrophy and lymphocytic hypoplasia in chronic myeloid leukemia. In this disease a profound peripheral lymphopenia is the rule, which reflects the reciprocal cell relationships as found in the hemopoietic tissues. Again, in certain patients showing pan-marrow hypoplasia, with anemia, lymphocytic leukopenia, a mild lymphadenopathy, and the presence of a scattering of lymphocytes in the otherwise aplastic bone marrow, this spontaneous "pseudoleukemic" myeloid-lymphoid reciprocity has at times raised the question of specifically stimulated lymphatic hyperplasia.

Reports of an occasional toxic disturbance of normal marrow function during sulfanilamide medication are appearing in the medical literature. One such instance in our own experience serves to emphasize the difference in character and in time relationships of the various marrow element responses when such a reaction occurs. A 66 year old, colored, male patient entered the hospital, on the fifth day following mild trauma, critically ill with a proven beta-hemolytic streptococcus

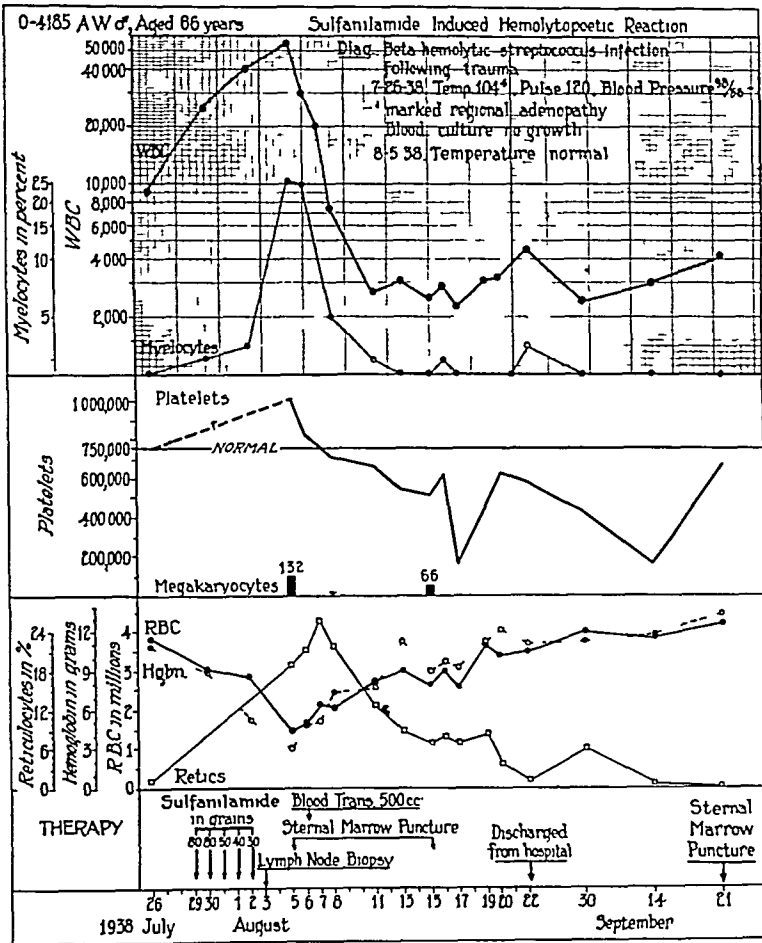


Fig 10

This patient illustrates the difference in type degree and time relationships of the reaction of the various bone marrow elements to the same toxic agent. At the point of maximum hemolysis, with red cells at a million and a half, hemoglobin 3 gms., and a spontaneous reticulocyte peak of 24 per cent, the total white cell count was 55 000 with 27 per cent myelocytes, and the platelets were over a million per c mm. By the time the red cells had again reached a normal equilibrium a persistent leukopenia and thrombocytopenia had developed. See Table 2 for the correlation of peripheral blood and sternal bone marrow data taken at representative periods.

infection involving the affected extremity and the regional lymph nodes. The total white cells were only 9000 per c mm, granulocytes 85 per cent with 11 per cent band forms and numerous toxic granule cells, red cells and reticulocytes were within normal limits. Sulfanilamide was administered in diminishing dosage as indicated in Fig 10 for 5 days, during which period clinical improvement was prompt and striking, and coincided with a marked rise in circulating white blood cells to a high point of 55,000, with 65 per cent neutrophilic granulocytes, 25 per cent

TABLE II

(To be studied in relation to Fig 10 and the text)

**SULFANILAMIDE INDUCED HEMOLYTOPOIETIC REACTION****Serial Sternal Bone Marrow Biopsies**

Patient A W Aged 66 years, colored, ♂  
 Diagnosis Beta hemolytic streptococcus infection following trauma  
 Marked regional adenopathy Blood culture—no growth

1938 August 5 August 15 September 21

**BLOOD**

Total WBC	55,000	2,500	4,250
Total RBC	1,570,000	2,660,000	4,250,000
Total Platelets	1,070,000	526,680	680,000
Hemoglobin	3 gm /100 cc	9 gm /100 cc	13.2 gm /100 cc
Reticulocytes	19.8	7.4	0.2
Supravital Diff			
PMN	65%	60%	58%
PMB	0	—	1
Myelocytes	27	0	0
Monocytes	0	10	8
Lymphocytes	8	30	33

**BONE MARROW**

Supravital Diff	First Biopsy	Second Biopsy	Third Biopsy
PMN	73%	48%	46%
Neutrophilic "C"	22.5	18	36
"B"	2	2	0
"A"	0	2	0.5
PMB	0.5	2	0.5
PMF	1	6	0.5
Eosinophilic "C"	0	0	0.5
"B"	0	0	0.5
Myeloblast	0	1	0
Lymphocyte	0	14	13.5
Monocyte	0	0	0.5
Plasmacyte	1	5	0.5
Plasma Cell	0	2	1
WBC Ratio	27%	29%	74%
Normoblast	68%	50%	44%
Erythroblast	32	50	56
Megakaryoblast	0	0	0
RBC Ratio	73%	71%	26%

250 grains sulfanilamide given orally in 5 days (July 29-Aug 3)

of which were myelocytes. The platelets were found at this time to be somewhat higher than normal. The red cells meantime had fallen sharply to a million and a half, the hemoglobin to 3 gms per 100 cc, while the reticulocytes, reflecting an increased spontaneous compensatory marrow delivery of new young erythrocytes, had risen to 19.8 per cent. As the red cells rapidly increased on the rebound, the leukocytes fell to a definite leukopenic level, which was maintained for some 6 weeks thereafter. The platelets paralleled the falling white cells and remained below normal for a comparable period. On the first two sternal marrow studies, the myeloid cells represented less than 30 per cent of all nucleated cells encountered, while by September 21 the proportion of erythroid to myeloid elements had again returned to normal. Thus, there were stimulatory, inhibitory and destructive phases in the reactions, differing in degree and duration with the cell types involved. In this instance one may hypothesize the sulfanilamide as increasing the effectiveness of, and the need for phagocytic leukocytes, at the same time diminishing the toxic myeloid inhibiting effects of the streptococci, conversely, the drug proved hemolytic for red cells in this individual in the dosage given, with the development of an acute, transitory anemia. Following the subsidence of the infection and the elimination of the therapeutic drug, the marrow returned more or less promptly to its original equilibrium.

Much more information needs to be accumulated relative to the white cells before we shall be in a position to influence their life cycles at the source as beneficially as is now possible for the red blood cells. At the moment, the important fact is their apparent independent response to various physiologic and pathologic influences, and their separate, even though closely related, functional specificities and capacities.

### THE HEMOLYTOPOIETIC EQUILIBRIUM

It must be clear to anyone familiar with the so-called hemolytopoietic equilibrium, that the problem is only a little more than half solved when the cell production end of the mechanism alone has been considered. Optimum peripheral distribution and minimal destruction of the cells once delivered to the circulation are fully as important for the maintenance of health. The spleen acts physiologically as the chief sequestration and reservoir organ for the blood cells, and its normal content of phagocytic plasma tocytes is greater proportionately, and in the aggregate, than any other organ in the human body. This furnishes the back-

ground for the well known splenic function of senile cell disposition, but at the same time sets the stage for a series of disease entities dependent upon the pathologic overdevelopment of one or more of these normal "graveyard" functions. In congenital hemolytic icterus, if the spectacular clinical recovery which follows successful splenectomy,<sup>29</sup> is correctly interpreted, it is this surgical removal of an organ with an inherited tendency to excessive hemolysis, rather than any direct attack on bone marrow deficiency or inadequacy, which restores the cellular equilibrium. The bone marrow is hyperplastic for red cells at the late erythroblast and normoblast levels of maturation during active anemic episodes with jaundice, and in the absence of all splenic tissue, the marrow has been proved to be entirely competent to maintain a normal cellular balance, adequate for health and for resisting successfully infection, despite red cell size or fragility abnormalities.

In certain instances of thrombocytopenic purpura where the marrow can be shown to contain the usual, or excessive numbers of qualitatively normal megakaryocytes, the successful removal of the spleen restores promptly and permanently, an adequate supply of functionally normal platelets to the circulation.<sup>40</sup>

Finally, in selected patients showing a profound granulopenia of otherwise undetermined etiology, with or without hepatic cirrhosis, but practically always with a marked splenomegaly, a more or less specific phagocytosis of granulocytes by excessive numbers of clasmotocytes can be demonstrated, both histologically in the excised splenic tissue, and clinically through the subsequent restoration of a normal peripheral white cell count and differential, the bone marrow having been found to be hyperplastic for myeloid cells in each patient throughout the preoperative leukopenic episode.<sup>41</sup>

Thus, when any deficit occurs in the essential blood elements in the peripheral circulation, and bone marrow studies reveal an hyperplasia of qualitatively normal precursors, the organ of origin is automatically cleared in the great majority of instances, and some peripheral etiologic factor or factors must be sought. The more extensive our knowledge of the specificity of functions and sensitivity of response of the essential cells of blood and connective tissues, the more effective should become the scientific control of the great variety of noxious states most of which influence profoundly and are thereby in turn significantly affected by the reactions of the cells we have been considering. The problems of

functional differentiation and morphologic identification are no longer of academic interest only. The accumulated information now available, at its best is life saving and specifically curative when intelligently and discriminatingly applied, at second best, it places clinical prognosis on a sounder scientific basis and points the way to the next steps wherein may lie the more complete answers to the many questions and problems still challenging solution.

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## THE CURIOUS CAREER OF TYPHOID MARY\*

GEORGE A. SOPER

I N spite of the fact that Mary Mallon was the most famous typhoid carrier who ever lived, the world knows very little about her. There is the paper in which I announced her discovery, published in the *Journal of the American Medical Association*, June 15, 1907, and the article in which I traced her career up to her final incarceration by the City of New York, eight years later, published in *The Military Surgeon* for July, 1919, but in the innumerable printed references which have appeared in the last thirty years these authoritative sources have generally not been fully utilized. Errors have been committed where one would least expect them and, these being copied and sometimes elaborated on, there have been woven accounts which depart materially from the facts. In my way of thinking the truth about Typhoid Mary is far more interesting than the tales which have been imagined about her, and as all the essential facts have not yet been told, I am glad to tell you some of the things which I think medical men may be interested in.

I first saw Mary Mallon thirty-two years ago, that is, in 1907. She was then about forty years of age and at the height of her physical and mental faculties. She was five feet six inches tall, a blond with clear blue eyes, a healthy color and a somewhat determined mouth and jaw. Mary had a good figure and might have been called athletic had she not been a little too heavy. She prided herself on her strength and endurance, and at that time and for many years thereafter never spared herself in the exercise of it. Nothing was so distinctive about her as her walk, unless it was her mind. The two had a peculiarity in common. Those who knew her best in the long years of her custody said Mary walked more like a man than a woman and that her mind had a distinctly masculine character, also.

I think Mary was born in the north of Ireland. She could write an excellent letter, so far as composition and spelling were concerned. She wrote in a large, clear, bold hand, and with remarkable uniformity. She

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read a good deal in the days of her captivity and seldom missed her daily paper

At the time I knew her, Mary had no home. If she had relatives or friends in this country or Europe, she never revealed the fact. Twice I thought I talked with a sister, once in Bridgeport, Connecticut, where my investigations carried me, and once in Brooklyn, but I could not prove it. At the time of her death relatives were advertised for in two newspapers for one month, by order of the Surrogate of Bronx County, and a lawyer was appointed to protect their interests, for Mary left a little money, but none appeared. None ever came forward when she was sick or in other trouble, and she never sent for any.

My discovery of Typhoid Mary was the outcome of an investigation made in the winter of 1906-'07 into an outbreak of typhoid fever in the house of Mrs. George Thompson, at Oyster Bay, N. Y., the preceding summer. The place had been rented to a New York banker, General William Henry Warren, who had occupied it with his family of three, and seven servants for the summer months. Late in August an explosion of typhoid had occurred in which six of the eleven persons in the household were taken sick. The epidemic had been studied immediately after it occurred by persons who were regarded as experts, and there were a number of typewritten reports upon it, but the cause had not been positively ascertained. It was thought by the owner that unless the mystery could be cleared up, it would be impossible to find tenants for the coming season.

It will be remembered that in those days typhoid fever was far more common than it is today and that the knowledge of its transmission was less complete. The reported cases in New York City in 1906 were 3,467 and the reported deaths, 639. The actual amount of typhoid was probably much greater.

Typhoid was believed to be due generally to polluted water or milk, or, in the opinion of some, to putrefying organic matter and sometimes to sewer gas. A paper was presented before the Royal Society by Horrocks at the end of 1906, in which he reported that typhoid and other bacteria might be carried by sewer air after being disengaged from the sewage or walls of the sewers, and the *Journal of the American Medical Association* declared that this possibility should be remembered.

At the end of the century typhoid epidemics occasionally of hundreds of cases, were occurring in different parts of the country. They

The idea of carriers was not entirely new to me. I had taken care to guard against carriers — urinary carriers — in my epidemic work. As is well known, a considerable percentage of convalescents pass a highly infected urine for many weeks after they are sufficiently recovered to go about, so I had had urotropin put up in convenient form to administer and issued an order that no patient might be discharged from medical attention until his urine was proved to be bacillus-free.

It was hard to identify typhoid in the feces by current bacteriological methods. I had read an address which Koch had delivered in 1902 on typhoid investigations in Trier which were based on a paper by Conradi and Drigalski in the same year, setting forth results they had obtained with a new culture medium in examining the stools of apparently well persons. A *Festschrift* on the sixtieth birthday of Koch, which appeared in 1903, contains several papers on the probable role of healthy carriers in producing typhoid, and publications by others in Germany were to like effect. Most of these I had not seen until Dr Simon Flexner called my attention to them after I had concluded my work on the Mary Mallon case.

Nothing of the kind had been done in America and the discovery of Typhoid Mary brought to light for the first time in America, or any other English-speaking country, a chronic typhoid carrier with infected feces. This type of carrier is now regarded as by all means the most common.

Having undertaken to see if there had been any carriers in the Oyster Bay house before the outbreak there occurred, I soon came, through the process of exclusion, to the cook. But where was she? She had left soon after the epidemic and that event had occurred over six months ago. I tried to find out everything I could about her, but there was not much to learn. Mrs Warren said she was a good plain cook, her wages were forty-five dollars a month, and she had been obtained from Mrs Stricker's. Stricker's was a well-known employment agency on Twenty-eighth Street. The cook had not fraternized with the other servants and they knew little about her. She was not particularly clean. Her name was Mary Mallon. That was about all.

But some of the details were of great significance. The cook had come to work on August 4, the first person fell ill August 27, and the first September 3. It seemed probable that all of the patients, the dates of whose attacks fell within a period of seven days, were infected at the